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BRITISH MEDICAL JOURNAL

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CLINICAL ASPECTS OF CARDIOMYOPATHY

BY

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[WITH SPECIAL PLATE]

The term "cardiomyopathy" has come into use to describe disorders of the heart not due primarily to rheumatic, hypertensive, coronary-artery, thyroid, or congenital disease. It is often assumed that cardiomyopathies are rare diseases; but, while this is true of some, recent work has tended to suggest that a number of cardiomyopathies may be commoner than previously thought. Nevertheless, despite increased awareness of the condition, we remain extremely ignorant of the causation of most of the cardiomyopathies.

No definition of the cardiomyopathies is entirely satisfactory, but the following is proposed as being generally useful. "Cardiomyopathy—a subacute or chronic disorder of heart muscle of unknown or obscure aetiology, often with associated endocardial, and sometimes with pericardial, involvement, but not atherosclerotic in origin."

Cardiomyopathy may be classified in many ways. The object of the present communication is to suggest a general classification for cardiomyopathy and to emphasize especially the methods of clinical presentation of this condition, basing conclusions on data derived from patients studied personally. So far as is possible the pathology has been correlated with the clinical presentation, with electrocardiography and radiology, and with the results of special investigations, such as angiocardiography and cardiac catheterization. No attempt has been made to give a full classification of all causes of cardiomyopathy.

Patients Studied

Sixty-six patients have been studied at Hammersmith Hospital, some of them in conjunction with our colleague, Dr. Donald Teare, of St. George's Hospital. Necropsy data have been available for most of these patients, but in some cases the clinical studies have been retrospective. Table I shows the pathological classification in the 66 cases studied, but does not necessarily indicate the relative frequency of the various types in the general population. There were 20 patients in whom cardiomyopathy was associated with, but not necessarily due to, a generalized disease such as carcinomatosis, a generalized infection, or a hypersensitivity state. Twelve patients did not have any associated general disease; in 7 of these there were characteristic pathological appearances such as endomyocardial fibrosis or endocardial fibroelastosis; in the other 5 the myocardial changes were non-specific. In the third group of 7 patients the heart was involved by a generalized disease such as amyloidosis, diffuse sclerosis (scleroderma), haemochromatosis, or leukaemia. Finally, there were 27 patients in whom a pathological or clinical diagnosis of asymmetrical hypertrophy of the heart had been made (Teare, 1958; Goodwin *et al.*, 1960; Hollman *et al.*, 1960). This condition, the pathology of which will be discussed later, produced evidence of obstruction to inflow or outflow of some part of the heart. The majority of patients showed evidence of obstruction to left ventricular outflow, thus simulating aortic stenosis. A smaller number showed some evidence of obstruction to right ventricular inflow, simulating tricuspid stenosis, and the minority showed evidence of obstruction to right ventricular outflow or left ventricular inflow. On the basis of these findings we suggest that cardiomyopathy may arise in three principal ways: (*a*) in association with

TABLE I.—*Pathological Classification of 66 Cases of Cardiomyopathy*

1. Associated with general disease

	No. of Patients
Carcinomatosis	4
Cirrhosis of liver	2
Infection	7
Hypersensitivity	4
Puerperal	1
Aplastic anaemia	1
Migrating thrombophlebitis	1
Total	20

2. Without associated general disease

	No. of Patients
Non-specific	5
Endomyocardial fibrosis	2
Familial	1
Endocardial fibroelastosis	1
Localized cardiac damage	3*
Total	12

3. Cardiac involvement by generalized disease

	No. of Patients
Amyloid	1
Scleroderma	2
Polyarteritis nodosa	2
Haemochromatosis	1
Leukaemia	1
Total	7

4. Asymmetrical hypertrophy (obstructive cardiomyopathy)

	No. of Patients
Right ventricular inflow	9
Right ventricular outflow	3
Left ventricular outflow	14
Left ventricular inflow	1
Total	27

* 2 with cardiac infarct, 1 with anomalous coronary artery.

*Frank Forman Medical Foundation Fellow, University of Capetown.

some generalized disease; (*b*) without generalized disease and without specific pathology; (*c*) of unknown aetiology, but often with characteristic pathology.

TABLE II.—*Clinical Types of Cardiomyopathy*

	No. of Cases
Type 1: Congestive heart failure often with atrio-ventricular valvular incompetence	
Simulating ischaemic heart diseases; "heart failure of uncertain aetiology"	35
Type 2: Obstructive	
Simulating stenotic valvular disease—principally aortic	27
Type 3: Constrictive	
Simulating constrictive pericarditis	4
Total	66

Clinical Presentation (Table II)

Clinically the patients could be divided into three types according to the effect of the cardiac disease upon the function of the heart. There was not a close correlation between the clinical types and the pathological groups except in the case of asymmetrical hypertrophy and obstructive cardiomyopathy. The commonest mode of presentation (which occurred in 35 cases) was that of persistent congestive heart failure with a large heart, gallop rhythm, and often pansystolic murmurs indicating mitral or tricuspid valvular insufficiency.

The second type presented with evidence of obstruction to cardiac flow, usually simulating aortic stenosis. In this group ejection murmurs suggesting obstruction to flow were common, except in those patients with evidence of obstruction to inflow of the right ventricle, in whom diastolic murmurs of tricuspid character were sometimes heard. There were 27 cases of this type, which corresponded to the pathological group described as asymmetrical hypertrophy.

The third and least common type simulated constrictive pericarditis; systolic murmurs were trivial or absent, and the heart was not usually as large as that found in the type with congestive heart failure.

With regard to the first and third types, patients may at some time show both constrictive and congestive types of clinical manifestations, depending on the development of further changes in the heart with progression of the disease. It is considered that the constrictive presentation is due to a tight and rigid myocardium which fails to relax in diastole, thus simulating the tight constriction of the heart in constrictive pericarditis. This type of presentation has been described in patients with myocardial fibrosis (Robin and Burwell, 1957; Nye *et al.*, 1957) and in amyloid disease (Hetzel *et al.*, 1953; Brigden, 1957). Other important factors in this group are probably endocardial sclerosis contributing to the myocardial stiffness, and in some cases involvement of the pericardium also. Intraventricular thrombosis is known to occur in cardiomyopathy, and systemic embolism is not unknown. Thus intramural thrombosis may well organize, giving rise to fibrosis and contributing to rigidity of the heart's action, so that a patient after initially presenting with congestive heart failure might proceed to the constrictive picture with the development and organization of intramural thrombus. For example, endomyocardial fibrosis either may present as congestive heart failure with mitral or tricuspid insufficiency or simulate a pericardial effusion or constrictive pericarditis (Williams and Shaper, cited by Davies, 1960). A constrictive pattern may very occasionally be seen in ischaemic heart disease, but usually yields to that of tricuspid incompetence.

The three clinical types will now be discussed in detail.

Type 1: Congestive Heart Failure Often with Atrio-ventricular Valvular Incompetence

This type was encountered most commonly, but in a number of cases only a retrospective study of the clinical records was possible. Exact clinical details were therefore not always available, but the over-all clinical picture will be made the subject of a more detailed report later. Cases occurred with specific disorders, such as scleroderma, or with non-specific myocardial pathology which in 20 cases was associated with a generalized systemic disease (Table I). The onset in these patients was very variable but usually insidious, and the duration of the disease varied from a few days to several years, usually being in the region of one year. Dyspnoea was almost invariable, being usually confined to effort, but sometimes paroxysmal in nature. Cardiac pain occurred in a small number of cases, and it is thus not surprising that such patients were often regarded as having ischaemic heart disease. On examination there were signs of congestive heart failure with oedema, raised jugular venous pressure, and often tricuspid incompetence shown by a systolic wave with sharp *y* descent in the venous pulse. The heart was usually considerably enlarged, sometimes grossly so, and gallop rhythm was common. Sometimes four heart sounds were heard, but a summation gallop was most common. The heart sounds were often quiet and muffled, and pericardial effusion had occasionally to be considered in the differential diagnosis. Pansystolic murmurs of both tricuspid and mitral incompetence were not uncommon. The murmur of tricuspid incompetence was heard best in the tricuspid area, and usually, though not always, increased on inspiration; that of mitral incompetence was heard at the apex and tended to decrease or not to alter with inspiration.

The arterial pulse was usually small, and atrial fibrillation occurred in about one-third of the cases. Neither these murmurs nor any other physical signs necessarily gave a clue to the aetiology, except in cases where the disease which affected the heart muscle also gave signs elsewhere in the body, such as haemochromatosis.

Radiology of the heart showed considerable or gross cardiac enlargement, sometimes with pleural effusions, and with the pulmonary vascular patterns associated with heart failure and pulmonary hypertension. Calcification within the heart or in the pericardium was not seen. The electrocardiogram commonly showed low voltage, with flat T waves and evidence of biventricular hypertrophy. Bundle-branch block and atrio-ventricular block were not uncommon, and atrial fibrillation occurred in about one-third of the patients. The blood picture showed no specific features, except for an eosinophilia in three cases. The biochemistry was essentially normal.

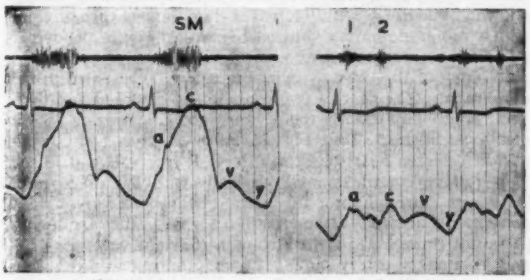
This type will now be illustrated by a case report.

Case 1

A woman aged 72 developed dyspnoea on effort in 1939 which became slowly progressive; she also noted mild Raynaud's phenomenon in the hands. In 1952 she was admitted to Hammersmith Hospital in congestive heart failure, which responded to treatment. At this time angiomata and cyanosis of the face and lips were noted. The arterial oxygen saturation was 95%. Her vital capacity was only 2 litres. In 1953 she lost weight and developed steatorrhoea. Both liver and spleen were enlarged at this time. In 1956 dysphagia for solid foods began, and in 1957

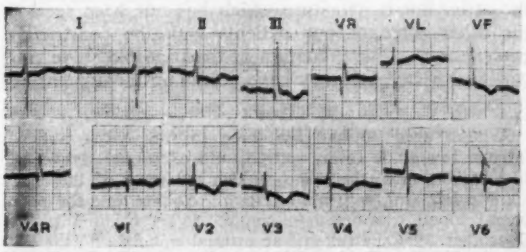
dyspnoea became even more severe and oedema of the abdomen and legs developed. It was elicited that a sister had died of cardiac failure of unknown cause.

Examination showed an elderly, frail lady with tight, shiny skin on the face and fingers and multiple telangiectases on the face. There was marked cyanosis of the face and digits, with moderate dependent oedema. The pulse was 60 to the minute, regular, and of small volume. The blood-pressure was 90/70 mm. Hg. The jugular venous pressure was 15 cm. above the sternal angle, with distended external jugular veins and a dominant *v* wave with sharp *y* descent (Text Fig. 1). The cardiac impulse was diffuse, the apex-beat being localized in the sixth intercostal space, just inside the anterior axillary line. A pansystolic murmur increasing on inspiration was present at the left sternal edge and radiated towards the apex (Text Fig. 1). There was ascites,



TEXT FIG. 1.—Jugular venous pulse, electrocardiogram, and phonocardiogram in Case 1. The pansystolic murmur (SM) and the large systolic (c) wave are seen to be increased on inspiration. (1=first heart sound; 2=second heart sound.)

with enlargement of liver and spleen. Haemoglobin 12 g. per 100 ml.; W.B.C. 4,000 per c.mm. (polymorphs 79%). Blood cholesterol 116 mg. and blood urea 84 mg. per 100 ml. Urine normal. Radiology of the chest showed generalized cardiomegaly with poor pulsation. The right atrium and ventricle and main pulmonary arteries were especially enlarged. The gastro-intestinal tract showed poor oesophageal motility with loss of mucosal pattern, a small sliding hiatus hernia, and diverticulosis of the sigmoid colon. Radiographs of the hands showed osteoarthritis and slight peripheral calcinosis, and a skin biopsy revealed incorporation of sweat-glands in connective tissue. The electrocardiogram (Text Fig. 2) showed Grade III right



TEXT FIG. 2.—Electrocardiogram of Case 1. There is a dominant R wave in leads V4R to V6 with right axis deviation, and an RS pattern in V5, indicating Grade 3 right ventricular hypertrophy. The low voltage and T-wave inversion in the chest leads is consistent with a generalized myocardial disorder.

ventricular hypertrophy with low voltage in the chest leads. The inverted T waves in precordial leads were considered to be due either to right ventricular hypertrophy or to a generalized myocardial disorder.

A diagnosis of generalized scleroderma was made, but the congestive heart failure progressed to a fatal outcome despite treatment.

Pathology (Special Plate, Fig. 1; Table III).—The heart showed right ventricular enlargement with areas of refractile fibrillary replacement fibrosis of the myocardium. The endocardium and pericardium were both normal. The tricuspid valve ring was stretched. The small pulmonary arteries showed some degree of sclerosis.

TABLE III.—*Pathological Details of the Hearts of Cases* 1-3

Case No.	Heart Weight (g.)	Left Ventricle	Right Ventricle	Circumference of Tricuspid Valve Ring (mm.)	Circumference of Mitral Valve Ring (mm.)
1	442	Normal	Hypertrophied (5 mm.)	130	100
2	495	Hypertrophied (21 mm.)	Hypertrophied (7 mm.)	115	85
3	365	Normal	Hypertrophied (6 mm.)	135	85

COMMENT.—In this case severe sclerosis of the myocardium in association with generalized systemic sclerosis and scleroderma led to progressive cardiac failure with cardiac dilatation and tricuspid insufficiency. Mitral insufficiency was not noted. There was no endocardial or pericardial involvement, and the pattern of cardiac constriction did not occur, presumably because fibrotic replacement led to progressive dilatation of the heart and poor contractility. Though the cause of diffuse sclerosis is unknown, the clinical diagnosis was obvious in this patient before death and the method of heart failure was clear. The sclerosis of the small pulmonary arteries caused pulmonary hypertension, which explained the large main pulmonary arteries and the cardiographic signs of right ventricular hypertrophy, and contributed to the tricuspid incompetence and heart failure.

Type 2: Constrictive Cardiomyopathy

The four patients of this type will be illustrated by case reports.

Case 2

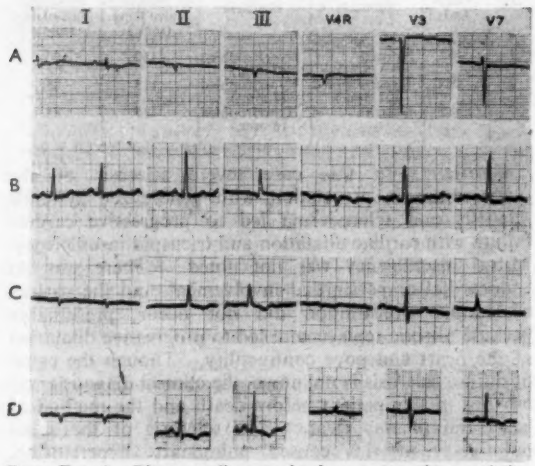
A woman aged 55 complained of angina of effort for one year accompanied by dyspnoea on exertion and oedema of the ankles. For two months she suffered from paroxysmal cardiac dyspnoea, and for two weeks from rapidly increasing dyspnoea on effort and oedema. Further and more protracted episodes of chest pain occurred subsequently. The past and family histories were non-contributory.

On examination there were orthopnoea at rest and extensive oedema with ascites. The pulse was 90 per minute, regular, and of small volume. The blood-pressure was 130/75 mm. Hg., and the jugular venous pressure 16 cm. above the sternal angle with large *a* and *v* waves with sharp *x* and *y* descents. The venous pressure increased on inspiration. A weak cardiac impulse was felt in the mid-clavicular line. The first and second heart sounds were soft, but a loud third heart sound was audible. There was basal congestion of both lungs, with a pleural effusion on the right side. The liver was enlarged four fingerbreadths below the costal margin, with slight presystolic pulsation. The tongue, finger-tips, and skin were all normal, and there was no rash. Haemoglobin 15 g. per 100 ml.; P.C.V. 48%; W.B.C. 9,000 per c.mm. (polymorphs 58%; eosinophils 11%). Biochemical tests showed: serum cholesterol 276 mg. per 100 ml.; serum glutamic oxalacetic transaminase 80 units (normal 16). The serum potassium varied from 3.6 to 6 mEq per litre, the serum sodium was normal, but the serum albumin was 3.4 g. and globulin 4.1 g. per 100 ml. Congo-red test negative; urine normal. Radiology of the chest (Special Plate, Fig. 2) showed generalized cardiac enlargement, a right-sided pleural effusion, and left-sided congestion with horizontal costo-phrenic lines, indicating pulmonary venous hypertension. The electrocardiogram (Text Fig. 3A) showed low voltage in limb leads, the T waves being flat or slightly inverted throughout. The deep

S waves in V5 and V2 suggested biventricular enlargement and possibly anterior infarction.

Cardiac failure persisted, and she died suddenly three months after admission, following an attack of cardiac pain.

Pathology (Special Plate, Fig. 5).—Both ventricles were enlarged (Table III). Extensive deposits of amyloid material were present in the myocardium around small vessels and



TEXT FIG. 3.—Electrocardiogram in four cases of constrictive cardiomyopathy. A. Case 2, showing low voltage, flat T waves, and deep S waves in leads V4R, V3, and V7. B. Case 4, showing ST depression in leads I, V3, and V7, and inverted T wave in V3. C. Case 3, showing low voltage, sinus tachycardia, and long PR interval (0.36 sec.). D. Case 5, showing low voltage and inverted T waves in leads II, III, and V7.

scattered through the interstitial tissue. There were also deposits of amyloid substance on the endocardium and pericardium. There was no evidence of amyloid anywhere else in the body.

COMMENT.—The attacks of cardiac pain and raised transaminase level suggested the presence of ischaemic heart disease with cardiac infarction, but the constrictive pattern in the jugular venous pulse led to the suggestion that the condition might in fact be due to constrictive pericarditis or cardiomyopathy. The lack of great cardiac enlargement, together with the haemodynamic pattern, suggested the possibility of amyloid disease, and this diagnosis was made before death. The extensive involvement of the myocardium, together with that of the endocardium and pericardium, explained the pattern of cardiac constriction. Murmurs were absent and atrio-ventricular valvular incompetence did not occur. The cardiac pain and raised transaminase level may be explained by destruction of the myocardium and replacement with amyloid tissue. Though the amyloid surrounded the blood-vessels, their lumina were in fact clear, and occlusive coronary artery disease was absent.

This case illustrates the usefulness of the haemodynamic pattern in distinguishing amyloid disease of the heart from ischaemic heart disease.

Case 3

A man aged 46 years. In 1950 enlargement of the liver and spleen was detected prior to a haemorrhoidectomy. Symptoms were absent until 1953, when progressive tiredness, dyspnoea on effort, and swelling of the abdomen developed. For a few weeks there was vague tightness across the chest on effort and after meals. The family history was negative.

Examination showed a dark-skinned man with bruises on the skin. Hess's test was positive. There was a generalized slight lymphadenopathy. Ascites and firm, smooth, diffuse enlargement of the liver to the level of the umbilicus were present. The spleen was hard and moderately enlarged. The pulse was regular at 120 per minute and there was pulsus paradoxus. The blood-pressure was 130/95 mm. Hg, and the jugular venous pressure was raised to the angle of the jaw, with large *a* and *v* waves and sharp *x* and *y* descents. The cardiac impulse was impalpable and the heart sounds were faint, with a gallop rhythm due to a third heart sound. The lungs were clear. Haemoglobin 12 g. per 100 ml.; W.B.C. 9,000 per c.mm. (lymphocytes 73%, with atypical forms; polymorphs 25%; eosinophils 1%); platelets 30,000 per c.mm. Urine normal. Biochemistry showed serum albumin 3.1 g., globulin 3.5 g., urea 22 mg., and cholesterol 123 mg. per 100 ml. The electrolytes were normal. Bone-marrow biopsy showed an increased proportion of mature lymphocytes; liver biopsy showed reticulosis with increased lymphocyte production; and lymph-node biopsy showed hyperplasia with pleocytosis and fibrosis, suggestive of a Hodgkin's type of reticulosis. Radiology of the chest (Special Plate, Fig. 3) revealed a high diaphragm. The heart was not obviously enlarged and there was good pulsation; there was no calcification. The electrocardiogram (Text Fig. 3C) showed sinus tachycardia, and first-degree heart-block with a P–R interval of 0.36 sec. Low-voltage complexes in limb leads with flat or inverted T waves throughout suggested generalized myocardial disease. Cardiac catheterization gave the following pressures (mm. Hg): right atrium 14/6, right ventricle 42/7, and pulmonary artery 40/28. Cardiac output was 6.2 litres per minute. A pericardial effusion was excluded by passing the tip of the catheter to the border of the right atrium. A diagnosis of reticulosis with cardiac involvement was made.

Improvement followed treatment for the reticulosis and for heart failure, but atrial fibrillation developed, and he finally succumbed to an intercurrent infection.

Pathology (Special Plate, Figs. 6 and 7).—The right ventricle was enlarged and the tricuspid valve ring stretched (Table III). The myocardium showed a heavy, diffuse infiltration with abnormal lymphocytes, and fibrosis and oedema. The endocardium, and to a lesser extent the pericardium, were heavily infiltrated with lymphocytes.

COMMENT.—This patient suffered from a reticulosis which involved the heart extensively, and the heavy infiltration of all three layers of the heart explained the signs of cardiac constriction. The development of atrial fibrillation must have been related to involvement of the atria, but is a feature which has not been seen in the other three of our patients with the constrictive presentation. The dilatation of the tricuspid valve ring was unexpected and may have been a terminal event.

Case 4

A man aged 30 had for three to four years noticed fatigue, low-grade fever, vertigo, and exertional dyspnoea. In October, 1955, there was sudden weakness of the right leg and left arm, with mild vertigo. At this time the peripheral blood was noted to contain 55% eosinophils. In December, 1956, he suffered an arterial embolism to the left leg, which was followed by intermittent claudication. From January to May, 1957, dyspnoea on exertion increased. Past and family histories were negative.

On examination the arterial pulse was 82 per minute, regular, and of normal volume. The blood-pressure was 160/100 mm. Hg, and the jugular venous pressure 15 cm. above the sternal angle, with marked *a* and *v* waves and sharp *x* and *y* descents. The cardiac impulse was quiet, with a slight right ventricular lift. A late third heart sound was heard along the left sternal edge. Both femoral pulses were weak and the posterior tibial pulses feeble; the left dorsalis pedis pulse was absent. The lungs were clear; the liver palpable, firm, and non-tender. The spleen was also palpable and firm. There was no ascites. The central

nervous system was normal, except for slight increase in knee- and ankle-jerks on the right side. The optic fundi and skin were normal. Haemoglobin 13 g. per 100 ml.; W.B.C. 10,000 per c.mm. (neutrophils 32%; eosinophils 43%); platelets 100,000 per c.mm.; E.S.R. 5 mm. in 1 hour. Blood urea, serum bilirubin, thymol turbidity, zinc sulphate, and acid phosphatase tests all gave normal results, and alkaline phosphatase was 39.5 and 25.5 mg. per 100 ml. respectively on two occasions. Serum cholesterol 240 mg. per 100 ml.; serum albumin 3.9 g. and serum globulin 3.9 g. per 100 ml. Complement-fixation test for toxoplasmosis negative. Urine normal.

Radiology of the chest (Special Plate, Fig. 4) showed considerable cardiomegaly involving mainly the right ventricle. Cardiac pulsation was sluggish, but there was moderate pulsation of the left atrium, which was slightly enlarged. Both pulmonary arteries were somewhat enlarged. The diaphragm and lung fields were normal. The electrocardiogram showed depressed ST segments in leads V3 to V6 and lead 1, with inverted T waves in V1 and V3 suggesting myocardial disease (Text Fig. 3B). Cardiac catheterization pressures (mm. Hg) right atrium, $a=24$, $v=24$, $x=7$, $y=10$. Pressures rose on inspiration. Right ventricle 37/12 and pulmonary artery 34/12 mm. Hg; pulmonary "wedge" pressure (mm. Hg), $a=23$, $v=22$, $x=9$, $y=10$, mean=15. Pressures rose on inspiration. Cardiac output 3.6 litres per minute. There was no intracardiac shunt. A raised pressure was thus demonstrated in both atria, and an early diastolic dip consistent with cardiac constriction was present in the right ventricle. Increase in pressure on inspiration was obtained in both right atrium and pulmonary "wedge" positions. All these findings were consistent with cardiac constriction, but did not indicate where the constriction might lie.

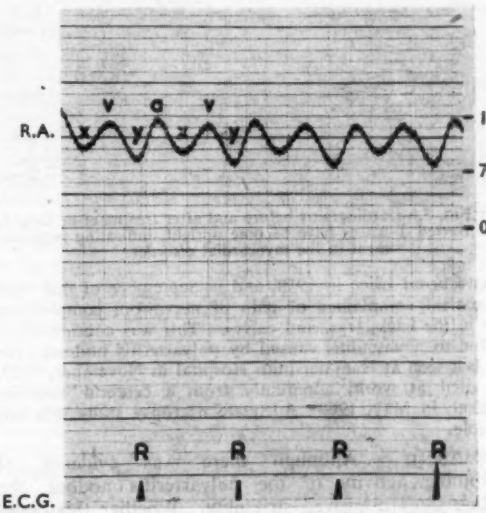
A diagnosis of constrictive cardiomyopathy was made. The eosinophilia, enlarged liver and spleen, and repeated neurological phenomena, together with evidence of peripheral arterial embolism, all suggested that constrictive pericarditis was not the cause. Polyarteritis nodosa was considered because of the eosinophilia, hypertension, and neurological signs, but it was thought that Löffler's "constrictive endomyocarditis" with endocardial thrombosis and subsequent emboli fitted the whole picture better.

Treatment with anticoagulants and steroids was instituted, but the patient has left the country and has not been seen since.

COMMENT.—In this case the evidence of constriction was clear, but the exact cause remains uncertain in the absence of necropsy data or further clinical manifestations of a generalized disease. The eosinophilia and evidence of endocardial thrombosis, however, would harmonize with the so-called Löffler's type of cardiomyopathy. In view of the eosinophilia and evidence of multiple emboli, treatment with steroids and anticoagulants was considered the best method of control.

Case 5

A man aged 52 complained of cough at night with slight exertional dyspnoea and tiredness for three years, increasing over the last year. For six weeks he had noticed swelling of the ankles. On examination in April, 1957, the arterial pulse was normal, without paradox. The jugular venous pressure was 15 cm. above the sternal angle, with marked *a* and *v* waves with sharp *x* and *y* descents (Text Fig. 4). The cardiac impulse was diffuse and the pulsation quiet. There was a loud late third heart sound heard at the left sternal edge, but no murmurs. The blood-pressure was 130/75 mm. Hg, and there were bilateral pleural effusions and basal rales. The liver was enlarged to the umbilicus, with a firm edge but no pulsation. There was no oedema. Haemoglobin 15 g. per 100 ml.; W.B.C. 12,000–25,000 per c.mm., with the eosinophil count varying from 25 to 50%. The E.S.R., liver function tests, and electrolytes were all normal. No lupus erythematosus cells were found. The Congo-red test and toxoplasma agglutination tests were negative, as were the Wassermann and Kahn reactions. No disorder of blood-clotting was found. The blood urea was 24 mg. per 100 ml., calcium 4.6 mEq per litre, phosphate 3.1 mg. per 100 ml., bilirubin 1.3 per 100 ml., alkaline phosphatase 15.1 units, and acid formal stable phosphatase 4.2 units. The electrocardiogram (Text Fig 3D) showed low voltage and inverted T waves, suggesting a myocardial disorder. Bone-marrow biopsy showed eosinophilic hyperplasia, and liver biopsy showed central lobular congestion



TEXT FIG. 4.—Right atrial pulse (RA) in Case 5, showing equal *a* and *v* waves and sharp *x* and *y* descents, and elevated right atrial pressure. R=R wave of electrocardiogram. (Figures refer to pressures in mm. Hg.)

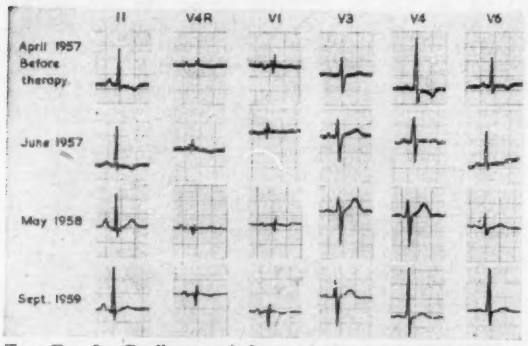
but was otherwise normal. No eosinophilic infiltration was seen. Radiology of the chest (Special Plate, Fig. 8A) showed slight cardiomegaly and bilateral pleural effusions. Cardiac catheterization: right atrial pressure (mm. Hg)—$a=13$, $v=15$, $x=7$, $y=8$; mean=11. The cardiac output was 2.3 litres per minute, and there was no intracardiac shunt (Text Fig. 4). It was not possible to enter the pulmonary artery, and pressures were not obtained from the right ventricle owing to persistent ventricular ectopic beats. The pressure rose in the right atrium on inspiration. The pattern was consistent with cardiac constriction, but did not indicate where the constriction might lie.

A diagnosis of constrictive cardiomyopathy with eosinophilia, possibly due to polyarteritis nodosa, was made. The patient was treated with a low-salt diet, digoxin, and mercurial diuretics, and by aspiration of the pleural effusions. The latter were pale in colour and contained 60% eosinophils. In view of the lack of cardiac enlargement, constrictive pericarditis was seriously considered, but the profuse eosinophilia seemed to make this diagnosis unlikely. Progress was stormy thereafter, for a generalized urticarial haemorrhagic rash appeared, which responded to steroid therapy. Signs of peripheral neuropathy developed, and there was a silent perforation of the small bowel, attributable to prednisolone and requiring surgical intervention. However, the rash cleared after cortisone was substituted for prednisolone.

A final diagnosis of polyarteritis nodosa, accounting for the peripheral neuropathy, rash, and cardiac involvement, was made. It was thought that the polyarteritis was involving the myocardium, producing constrictive cardiomyopathy, rather than involving the coronary arteries and producing ischaemic heart disease.

The patient remained well on digitalis and cortisone. The venous pressure fell to 5 cm. above the sternal angle, but

the constrictive pattern remained. The pleural effusions did not recur and the heart became smaller (Special Plate, Fig. 8B). Later the third heart sound disappeared and the jugular venous pressure fell to 3 cm. above the sternal angle. The cardiogram showed striking improvement (Text Fig 5). The



TEXT FIG. 5.—Cardiograms before and after treatment in Case 5. The inverted T waves have become upright, indicating improvement in the myocardial disorder.

rash recurred twice in 1959, and in September of that year the patient complained of pain of nerve-root compression type in the back, legs, and calves. This was considered to be due to a vasculitis caused by polyarteritis nodosa. He was last seen at Hammersmith Hospital in November, 1959, and died at work, apparently from a cerebral vascular accident, in May, 1960 Adequate necropsy study was not possible.

COMMENT. — Although there was evidence of continuing activity of the polyarteritis nodosa, the cardiac signs improved strikingly. Whether this could be attributed to treatment with steroids is not known, but the improvement is of considerable interest in view of the almost uniformly unsatisfactory nature of treatment for cardiomyopathy. It is interesting to speculate on the exact distribution of the pathological process within the heart, but it may be assumed that the myocardium was heavily involved and possibly the pericardium also.

Type 3: Obstructive Cardiomyopathy

The pathological features of this condition have been described by Teare (1958), and the two main clinical types, involving obstruction to the inflow of the right ventricle and to the outflow of the left ventricle respectively, have subsequently been documented (Goodwin *et al.*, 1960; Hollman *et al.*, 1960). Teare's original study was a pathological one, and illustrated patients who had died suddenly or in congestive heart failure and who at necropsy showed massive irregular asymmetrical hypertrophy of the ventricular septum with irregularly placed and grossly enlarged muscle fibres and bundles with interlacing interstitial fibrosis. One of his cases had been under the care of Hammersmith Hospital with signs suggestive of tricuspid-valve obstruction, and subsequently the patient's family were studied and found to have a high incidence of similar physical signs and other abnormalities suggesting mild tricuspid stenosis (Hollman *et al.*, 1960). It is believed that in these patients the irregular and asymmetrical hypertrophy of the septum was obstructing right ventricular inflow. In one of Teare's cases obstruction to left ventricular inflow by a massive septal hypertrophy simulated mitral stenosis. When the septum obstructs the outflow of the left ventricle the condition simulates aortic stenosis, but has certain important differences. A similar, though not necessarily identical, condition has been described by Brock (1957, 1959), by Bercu *et al.* (1958), by Morrow and Braunwald (1959), by Soulié *et al.* (1959), and by Brent *et al.* (1960).

Table I, section 4, shows the patients with this condition whom we have studied. Nine had evidence of obstruction to right ventricular inflow, and three to right ventricular outflow, two of the latter having signs suggesting that left ventricular outflow was also involved. Fourteen patients had obstruction to left ventricular outflow alone or principally, and one patient had apparent obstruction to left ventricular inflow.

We cannot say for certain without necropsy data whether all these patients have asymmetrical hypertrophy, but there is little doubt that they are suffering from a cardiomyopathy which produces obstruction to the flow of blood within the heart and therefore merits the term "obstructive cardiomyopathy." The majority of these patients have ejection murmurs suggesting aortic or pulmonary valve obstruction, and are sharply to be distinguished from patients with cardiomyopathy with atrio-ventricular valve insufficiency or with cardiac constriction.

Obstructive Cardiomyopathy Involving Right Ventricular Inflow

These patients will not be described in detail, since they have been documented by Hollman *et al.* (1960). They have shown a tendency to sudden death, short ejection murmurs down the left sternal edge, not uncommonly gallop rhythm, and soft early diastolic murmurs, together with a globular heart on fluoroscopy. The cardiogram has not been particularly specific, but most cases showed a *q* wave and inverted T wave in lead III, and in some left precordial leads were abnormal. These cases thus suggested mild tricuspid stenosis or Ebstein's syndrome.

Right Ventricular Outflow Obstruction

There were three cases in this group. In one the diagnosis of corrected transposition of the great vessels and pulmonary stenosis had been made, and at cardiotomy for relief of pulmonary stenosis a massive hypertrophied septum was discovered. The septum was greatly hypertrophied and bulged into the right ventricle in systole. The pulmonary valve was normal. A quantity of muscle was resected from the septum, the gradient was reduced from 110 to 42 mm. Hg, and after the operation the systolic ejection murmur virtually disappeared. Histology of the resected muscle showed hypertrophied muscle fibres. It was thought that this patient, therefore, was an example of asymmetrical hypertrophy, for there was certainly obstruction to right ventricular outflow below the pulmonary valve. The other two cases were of special interest in that they presented features suggesting both aortic and pulmonary stenosis, but being typical of neither. Since it is probable that this combination of physical signs may suggest the diagnosis, these two patients will be considered in detail.

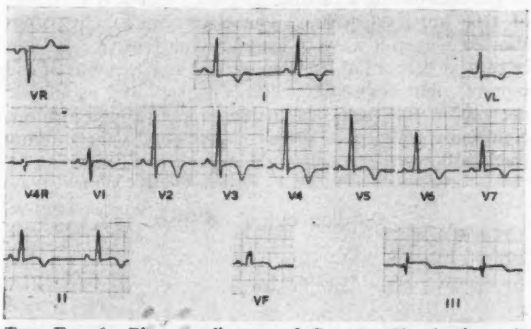
Case 6

A woman aged 37. At the age of 5 years a murmur was heard in the heart at a school medical examination. The patient said she had been breathless on extreme exertion from childhood, and at the present time could not run for a bus without dyspnoea. She had no syncope, but some

tightness across the chest on exertion. There was no past history of rheumatic fever.

Examination revealed a well-developed woman without cyanosis or clubbing of the fingers. The arterial pulse was small and regular, with occasional ectopic beats. The jugular venous pressure was 4 cm. above the sternal angle, with a prominent *a* wave and a sluggish *y* descent. The cardiac impulse consisted of a weak localized apex-beat in the fifth interspace in the mid-clavicular line. There were no thrills and no obvious right ventricular hypertrophy. There was a Grade 3 ejection systolic murmur, which was not quite full length and was loudest at the left sternal edge over the pulmonary artery. There were a faint scratchy diastolic murmur of doubtful aetiology at the left sternal edge and a late fourth heart sound. The pulmonary closure was very faint and delayed, aortic closure being easily heard. A systolic ejection click was heard on some occasions but not others.

Radiology of the chest showed enlargement of the right atrium, left ventricle, and pulmonary artery, and possibly of the right ventricle also. The heart was globular in shape, and the lungs and pulmonary vasculature were normal. The electrocardiogram (Text Fig. 6) was very unusual, with



TEXT FIG. 6.—Electrocardiogram of Case 6. The dominant R waves in leads V2 to V7, and in limb leads, with inverted T waves in all leads except VR, suggest hypertrophy of both ventricles and the septum.

dominant R waves in precordial leads V2–V7, and inversion of T waves from V4R to V7. The T waves were also inverted in leads I, II, III, and VF. The appearances were considered to be consistent with hypertrophy of both ventricles and of the ventricular septum. Cardiac catheterization did not reveal any intracardiac shunts, and the arterial oxygen saturation was 94% at rest and on exercise. There was a pressure gradient of 26 mm. Hg at the level of the pulmonary valve. Angiocardiography showed a very thick left ventricular muscle wall. The aortic sinuses and aorta were normal. There was a persistent deformity and narrowing of the infundibulum of the right ventricle, and the main pulmonary artery was enlarged, but the valve seemed normal. The ventricular septum appeared to be very large, and the infundibular region to narrow during ventricular systole. The left ventricle and ventricular septum were thought to bulge into the right ventricle below the pulmonary valve.

COMMENT.—Though some features, notably the murmur, the dilatation of the pulmonary artery, and the pressure gradient at valve level, suggested conventional pulmonary stenosis, there were many points against it. These were the small jerky pulse, the scratchy diastolic murmur, and the bizarre electrocardiogram, which seemed to be incompatible with simple pulmonary stenosis. The diagnosis was strengthened by the angiographic appearances suggesting a very large septum. However, the presence of the pressure gradient at valve level instead of in the body of the right ventricle, as has been found in other cases, was unusual. The final conclusion was that the patient was suffering from enlargement of the septum due to asymmetrical hypertrophy, which produced obstruction to right ventricular outflow and to some extent left ventricular outflow also.

The next patient is of special interest, since she showed an association of the condition with congenital heart disease and clear evidence of the progressive nature of obstructive cardiomyopathy.

Case 7

A girl aged 15 was first seen at the age of 7 in 1952. Her birth had been normal, but her mother had contracted rubella six weeks before pregnancy started. The patient was well until 8 months of age, and from then on had frequent respiratory infections and bronchitis every winter. Cyanosis had occasionally been seen. At the age of 2½ years a cardiac murmur was heard.

On examination there was no cyanosis or clubbing of the fingers, but the palate was highly arched. There was prominence of the left side of the chest, and a left ventricular type of impulse was noted in the fifth intercostal space 4½ in. (11.4 cm.) from the mid-line. A systolic thrill maximum at the fourth left intercostal space was felt, and there was a loud murmur maximum in the same area with a faint early diastolic murmur at the left sternal edge. The blood-pressure was 105/50 mm. Hg, and the arterial pulse was regular, quick-rising in nature, and of good volume. The jugular venous pressure was normal, as were the femoral pulses. Radiology of the chest revealed enlargement of the right ventricle and pulmonary arteries, with slight hilar pulsation and slight overfilling of the lungs. The electrocardiogram showed right and left ventricular hypertrophy. Cardiac catheterization pressures (mm. Hg): pulmonary artery 57/43, mean 47; right ventricle 57 (systolic). There was a left-to-right shunt at pulmonary-artery level, with a ratio of pulmonary to systemic flow of 1.7 : 1.

A diagnosis of patent ductus arteriosus was made, and a wide, short patent ductus was found and ligated by Mr. L. L. Bromley in 1952. After ligation the thrill disappeared, but in the post-operative period there was a persistent systolic murmur in the left second and third intercostal spaces. This murmur was attributed to aortic stenosis or possibly to residual pulmonary hypertension.

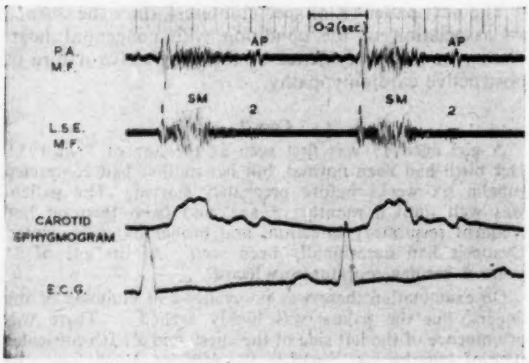
The patient lost all her symptoms, and for the next three years remained perfectly well. When reassessed in 1955 she was found to have a small, quick-rising arterial pulse, the cardiac impulse suggested enlargement of both ventricles, and there was a small *a* wave in the jugular venous pulse. The second heart sound was thought to be normal, but there was a Grade 4 systolic murmur maximal in the third left intercostal space. The electrocardiogram still showed evidence of hypertrophy of both ventricles.

In 1956 a further cardiac catheterization was carried out. No intracardiac shunt was discovered, but there was still evidence of pulmonary hypertension, though less severe than before. The mean right atrial pressure in mm. Hg, was 12, the right ventricle 42/5, and the pulmonary artery 42/16. There was no gradient across the right ventricular outflow tract.

At this point the possibility of mitral insufficiency associated with subaortic stenosis and fibroelastosis was considered.

In May, 1960, she was readmitted for further investigation. Her symptoms had not increased and she was able to undertake fairly heavy exertion without dyspnoea. Examination showed a moon face, but no cyanosis or clubbing of the fingers. The arterial pulse was jerky, of normal volume, and regular. The jugular venous pressure showed a 2-cm. *a* wave, but was otherwise normal. The cardiac impulse showed a marked lift over the right ventricular outflow tract. There was a systolic thrill at the left sternal edge, but not in the aortic area. A Grade 4 harsh ejection systolic murmur was heard at the apex and

the left sternal edge. The second heart sound was split 0.03/second (Text Fig. 7). There was a faint scratchy mid-diastolic murmur increasing on inspiration at the left sternal edge, and probably arising from the tricuspid valve.



TEXT FIG. 7.—Phonocardiogram of Case 7, showing a harsh diminuendo ejection murmur. The second heart sound is split 0.03 per second. SM=systolic murmur; A=aortic-valve closure; P=pulmonary-valve closure; 1=first heart sound; 2=second heart sound; LSE=left sternal edge; MF=medium frequency.

Radiology of the chest showed enlargement of both ventricles and right atrium. The heart was globular in shape and the lung fields normal (Special Plate, Fig. 9). The electrocardiogram showed little change. Cardiac catheterization pressures (mm. Hg): pulmonary artery 42/30; right ventricle 108/0; right atrium $a=20$, $v=12$, mean=10. There was a gradient of 60 mm. Hg low in the body of the right ventricle. The brachial artery pressure was 130/54 mm. Hg. No intracardiac shunt was found. Angiocardiography (Special Plate, Fig. 10) showed narrowing of the outflow tract of the right ventricle below the pulmonary valve, probably due to hypertrophy of the septum, and a massive ventricular muscle wall.

COMMENT.—These three patients illustrate the effect of cardiomyopathy on right ventricular outflow. It seems most unlikely that they are suffering from conventional pulmonary stenosis, and the combination of signs suggesting both aortic and pulmonary stenosis makes the diagnosis of asymmetrical hypertrophy very probable. These patients also illustrate two other important points: the association of the condition with congenital heart disease and the progressive nature of the condition, which has been suspected in our other cases.

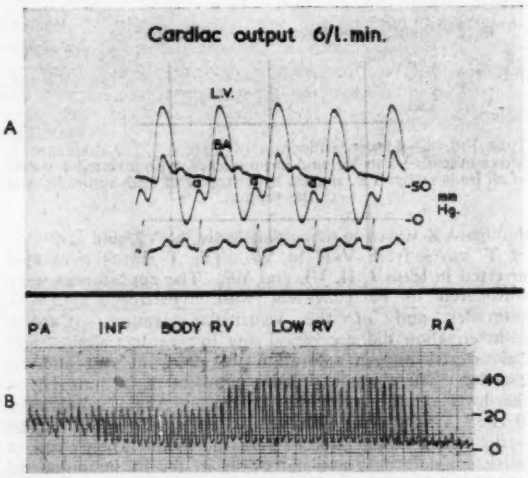
Left Ventricular Inflow Obstruction

Teare (1958) described a patient who clinically suffered from mitral stenosis, but at valvotomy was found to have a muscular mass obstructing left ventricular inflow. At necropsy this patient was found to have asymmetrical hypertrophy of the ventricular septum. We have seen but one case diagnosed clinically and on haemodynamic grounds, and we lack necropsy proof; we therefore cannot comment further on this group.

Left Ventricular Outflow Obstruction

We have described this group under the title of "Obstructive Cardiomyopathy Simulating Aortic Stenosis" (Goodwin *et al.*, 1960). A full description will therefore not be given again, but the salient features will be briefly commented on. These patients presented with a history exactly simulating aortic stenosis, anginal pain, syncope, and dyspnoea on exertion being common. We have seen the condition in childhood and in adult life and in both sexes. Of our 14 patients, 9 were men and 5 women. A familial tendency has also been noted. The physical signs consisted of a normal or jerky arterial pulse, a loud ejection murmur (and often a thrill) maximal at the left sternal edge rather than at the apex or aortic base. There was no calcification of the aortic valve, and dilatation of the ascending aorta was not usually a feature. These were the clinical signs of pure left ventricular outflow obstruction, but there were often some associated signs of obstruction to right-sided inflow or outflow also. Thus a prominent *a* wave in the jugular venous pulse was not uncommon, and we have noted a scratchy tricuspid diastolic murmur. An atrial sound was not uncommon, but an aortic diastolic murmur has never been heard. Reversed splitting of the second heart sound, so common in aortic stenosis, was unusual in this condition. The cardiac impulse tended to be more diffuse and quieter than the thrusting, strong left ventricular impulse found in true aortic-valve stenosis.

Radiology of the chest commonly showed a globular heart with enlargement of the right atrium as well as the left ventricle, but this was not necessarily so, a number of patients having a cardiac silhouette identical with that of true aortic stenosis. The electrocardiogram often showed a deep S wave in lead V5 and T-wave inversion in central precordial leads suggesting enlargement of the septum, right ventricular enlargement as well as left, or necrosis in the region of the septum. Catheterization, commonly revealed a pressure gradient in the outflow tracts of both left and right ventricles (Text Fig. 8).



TEXT FIG. 8.—A. Systolic pressure gradient between left ventricle (LV) and brachial artery (BA) in obstructive cardiomyopathy simulating aortic stenosis. B. Systolic pressure gradient in body of right ventricle in same condition. (The gradients are believed to result from bulging of the hypertrophied septum into both ventricles in systole.) PA=pulmonary artery; RV=right ventricle; INF=infundibulum; RA=right atrium.

That in the right ventricle was usually low in the body and quite unlike that of infundibular stenosis. Angiocardiography from the right side of the heart has revealed a normal aorta and aortic sinuses, but massive enlargement of the ventricular muscle, including the septum. Left ventricular angiography is probably necessary to delineate adequately the septum and outflow tract of the right ventricle, and we plan this in the future.

Results of Operation.—Further information about this group has been obtained at thoracotomy for relief of the outflow-tract obstruction. Three patients have been operated on. In the first (Case 1 (A. Je.), Goodwin *et al.*,

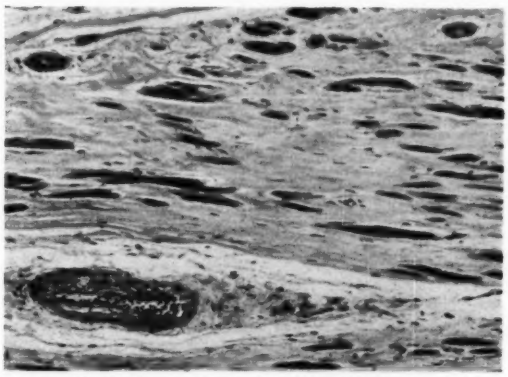


FIG. 1.—Photomicrograph of myocardium in Case 1. Extensive fibrosis can be seen, with strands of surviving muscle cells. (H. and E. ×97.)

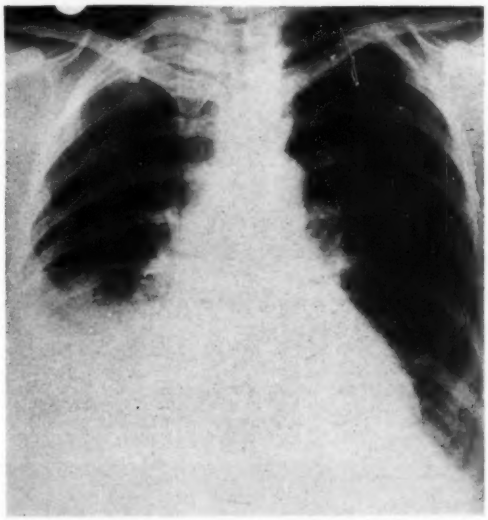


FIG. 2.—Six-foot postero-anterior radiograph of chest in Case 2, showing generalized cardiac enlargement and right pleural effusion.

FIG. 3.—Six-foot postero-anterior radiograph of chest in Case 3, showing virtually normal cardiac silhouette.

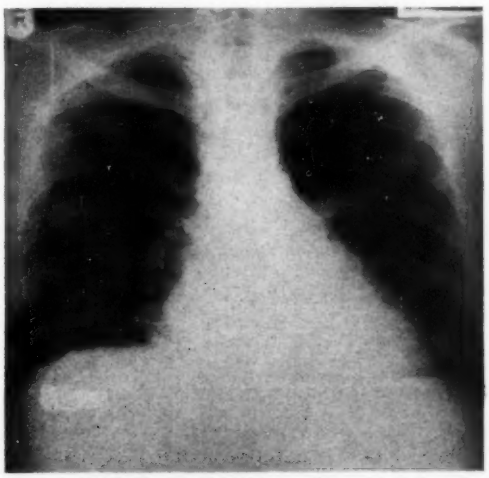


FIG. 4.—Six-foot postero-anterior radiograph of chest in Case 4, showing generalized cardiac enlargement.

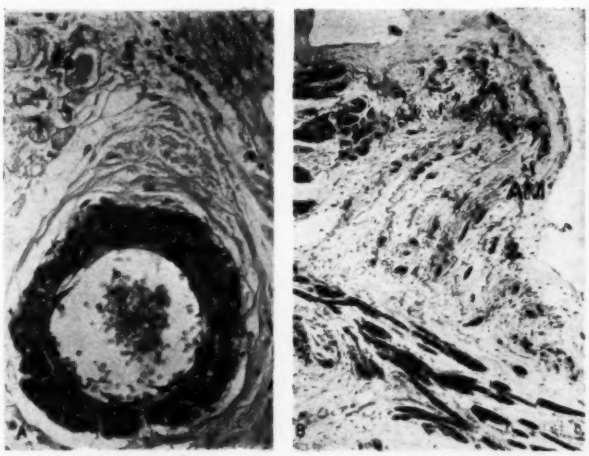


FIG. 5.—Photomicrographs of heart of Case 2. A. Myocardium, showing amyloid material in wall of small coronary artery. (H. and E. ×220.) B. Endocardium, showing extensive amyloid deposit (AM). (H. and E. ×59.)

FIG. 6.—Photomicrograph of myocardium of Case 3, showing fibrosis and infiltration with abnormal lymphocytes. (H. and E. ×97.)

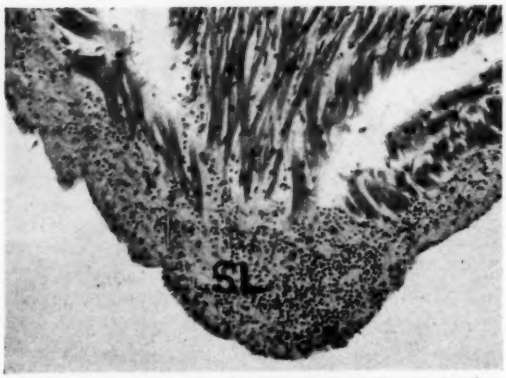


FIG. 7.—Photomicrograph of endocardium of Case 3, showing sclerosis and infiltration with abnormal lymphocytes (SL). (H. and E. ×97.)

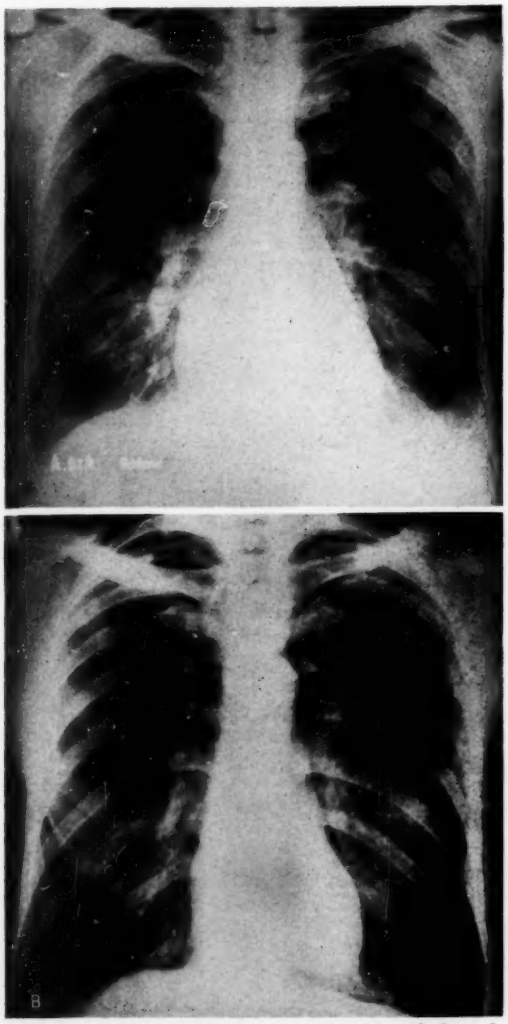


FIG. 8.—Six-foot postero-anterior radiographs of Case 5. A. Before treatment, showing bilateral pleural effusions, prominent pulmonary arteries, and slight cardiomegaly. B. After treatment, showing reduction in heart size and disappearance of pleural effusions.

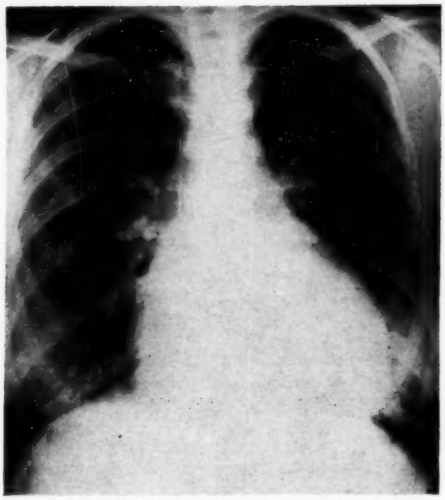


FIG. 9.—Six-foot plain radiograph of chest of Case 7, showing globular heart with enlargement of both ventricles and right atrium.

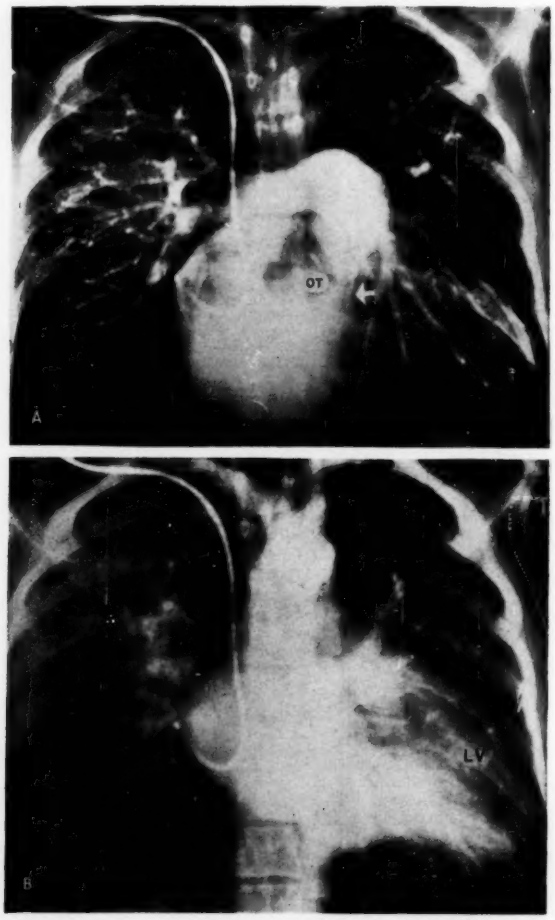


FIG. 10.—Venous angiocardiograms of Case 7. A. Postero-anterior projection, showing narrowing of right ventricular outflow tract (OT) below pulmonary valve. B. Postero-anterior projection, showing massive ventricular muscle wall (LV).

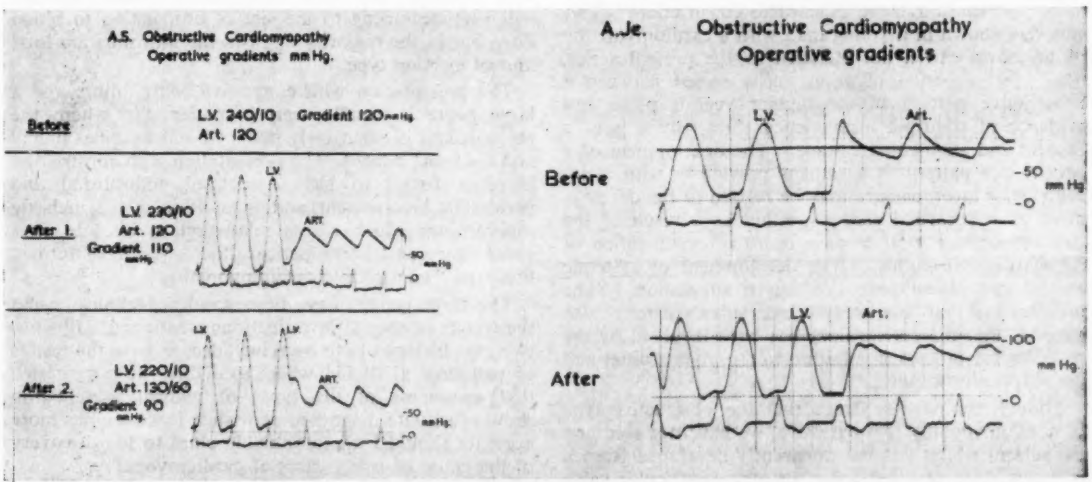
1960), when the left ventricle was explored from the aorta through the aortic valve the septum was found to be enormously enlarged and obstructing outflow. A portion of the septum was removed, and since this the patient has been free from angina, syncope, and dyspnoea. Histologically, the portion of ventricular muscle excised showed large muscle bundles. Though at left ventricular puncture before the operation a gradient between aorta and left ventricle of 60 mm. Hg in systole was discovered, at operation no gradient was found. Following the excision of the ventricular muscle, a small gradient developed, however (Text Fig. 9).

The second patient (A. S.) was found to have a substantial gradient both before operation and in the theatre immediately before the ventricle was explored. On opening the aorta and exploring the ventricle with the heart arrested no definite obstruction to outflow could be discovered. The septum appeared large, however, and a small amount of muscle was removed, but no localized obstruction could be found. Following closure of the aorta and re-starting of the heart the gradient across the outflow tract was only slightly reduced (Text Fig. 9). After the operation the physical signs were unchanged.

The third patient operated on resembled the first in that, though a substantial pre-operative outflow-tract gradient was found at left ventricular puncture, no gradient was found at operation. When the ventricle was explored the ventricular muscle was found to be extremely thick, but again there was apparently no localized hypertrophy of the septum. A small amount of muscle was excised, and after operation the systolic murmur became softer and shorter, but the pulse did not alter appreciably. The histology of the excised muscle in these two patients resembled that in the first.

The capriciousness of the gradients and the difficulty in demonstrating obstruction with the heart arrested are two of the most puzzling features of this condition. They presumably suggest that much of the obstruction is dependent on the way in which the hypertrophied septum functions during systole. We have already suggested (Goodwin *et al.*, 1960) that the character of the pulse might be due to late contraction of the hypertrophied muscle, so that the initial portion of the maximal ejection phase of the left ventricle is rapid. This would explain also the late onset of the systolic murmur. The lability of the gradient is also perhaps mirrored by the lability of the arterial pulse, for we have noted that the jerky nature of the pulse may vary from time to time. If the hypertrophied septum swings across in late systole to block the outflow tract, then it is possible that with the heart arrested no appreciable obstruction might be felt to left ventricular outflow. Some method is required of assessing the obstruction to outflow manually with the heart beating. The function of the septum could also be studied by left ventricular cine-angiography, which we propose to carry out in future.

Thus, while the condition of obstructive cardiomyopathy has clinically recognizable features, and while we believe that many cases are due to asymmetrical hypertrophy as described by Teare (1958), all cases are not necessarily due to this cause. The condition is now being widely described by various authors under different titles. Thus a clinical syndrome which is very similar has been described by Brock (1957, 1959) with the diagnosis of "functional obstruction of the left ventricle," while Bercu *et al.* (1958) used the term "pseudo-aortic stenosis." Morrow and Braunwald (1959) regard the condition as due to "functional aortic stenosis." Under the title of "Une cause d'erreur dans la diagnostique hémodynamique des rétrécissements aortiques," Soulié *et al.* (1959) described two cases in which obstruction to left ventricular outflow appeared to be due to asymmetrical hypertrophy of the septum. Brent *et al.* (1960) have studied members of two families suffering from left ventricular outflow-tract obstruction which they described as "familial muscular subaortic stenosis." Necropsy findings in three cases showed asymmetrical hypertrophy, the massive septum projecting into both ventricles. Brachfeld and Gorlin (1959) have described the syndrome of subaortic stenosis, and their cases in many respects resemble those of asymmetrical hypertrophy. There are, however, almost certainly a number of different conditions which can produce obstruction to left ventricular outflow below the valve. A diaphragm below the valve is well known, and this type of congenital subaortic stenosis may cause great difficulty in differential diagnosis from obstructive



TEXT FIG. 9.—Pressure gradients before and after resection of ventricular septum in two patients with obstructive cardiomyopathy simulating aortic stenosis. In A. Je. a small gradient has developed after resection, but in A.S. the gradient of 120 mm. before resection falls to 90 mm. Hg after resection.

cardiomyopathy. Björk (1960) has described two cases in which a subaortic stenosis was produced by an abnormally placed anterior leaflet of the mitral valve. It is of interest that in his cases the condition was clearly shown by left ventricular angiography. We believe, however, that the majority of cases of left ventricular obstructive cardiomyopathy with the characteristic signs that we have described are due to gross enlargement of the septum. When a gradient is found in the body of the right ventricle, this makes the diagnosis almost certain, for gradients in this situation are not, to our knowledge, found in other conditions. The nearest approach would appear to be the Bernheim syndrome, which possibly has some features in common with obstructive cardiomyopathy.

There is, however, still a great deal to be learned about the condition. Though we are now able to recognize it, we know nothing of its cause, except that there is a familial tendency, that the condition may be associated with congenital heart disease, and that it tends to increase with time. We believe also that there is a functional as well as an anatomical element, in view of the variable gradients and the findings at cardiotomy. It is conceivable that the condition starts as a disorder of function, perhaps as a neuromuscular imbalance of ventricular contraction with asynchrony of the septum and subvalvular regions, and that the gross hypertrophy and fibrosis are secondary phenomena. An infective cause has not been excluded.

Discussion

This study shows that patients with cardiomyopathy as defined by us may present in three major ways: (1) with cardiac dilatation, congestive heart failure, and atrio-ventricular valvular incompetence; (2) with signs of cardiac constriction; and (3) with signs of cardiac obstruction. A clinical differentiation into these three groups has some value, since it may aid diagnosis and occasionally prognosis. The recognition of the obstructive group may give a lead to successful surgical treatment, though it is too early to say whether this will in fact prove generally possible. The distinction between the two former types is not absolute, for patients may vary between the signs of atrio-ventricular valvular incompetence and those of cardiac constriction. This was well shown in a young man with a cardiomyopathy of unknown cause, not included in the present series, who over a period of four weeks varied between a constrictive pattern in the jugular venous pulse and evidence of tricuspid insufficiency shown by a poor *x* descent and augmented *v* wave. The development of a constrictive pattern in a patient previously with atrio-ventricular incompetence may be related to the development of endocardial changes, either as a result of the cardiomyopathy itself or as a result of organization of intracardiac thrombus. The development of systemic emboli would support the latter suggestion. The presence of an obviously constrictive pattern also suggests that the pericardium has been involved by the pathological process in addition to the myocardium and possibly endocardium.

Though we have evidence that the obstructive type of cardiomyopathy is progressive, we have not seen any patients in which this has apparently developed from a previous stage of constriction or atrio-ventricular valve incompetence. We think that this is probably a separate group and that overlap does not occur. The signs in the obstructive group appear to be dependent largely, if not entirely, upon the site of the obstruction, and are therefore remarkably specific. This is another reason for believing that obstruction in many of these patients is due to a specific asymmetrical hypertrophy of the septum, for in this way the simultaneous occurrence of obstruction to both outflow tracts and also to inflow tracts can be adequately explained. The diagnosis of obstructive cardiomyopathy should always be considered in any patient who has murmurs suggesting aortic stenosis but in whom the pulse is atypical. The maximum site of the systolic murmur and thrill down the left sternal edge is also of considerable importance. Patients who appear to have signs of both pulmonary and aortic stenosis should also be strongly suspected of suffering from obstructive cardiomyopathy. Where only right ventricular inflow is involved the signs are likely to be those suggesting tricuspid stenosis of mild degree or Ebstein's syndrome. However, cases with predominant left ventricular outflow obstruction may also show signs suggestive of right ventricular inflow obstruction, and this association may again prove a valuable diagnostic point.

Improved clinical diagnosis and study of all forms of cardiomyopathy should lead to clues as to aetiology in the various groups. Studies of affected families may also prove of considerable value, as may biochemical and other investigations, such as the quest for auto-immune and other antibodies.

Summary

An attempt has been made to classify clinically the cardiomyopathies according to three major clinical presentations: (1) a presentation with congestive heart failure and atrio-ventricular valvular incompetence, usually simulating ischaemic heart disease; (2) a presentation simulating constrictive pericarditis; and (3) a presentation simulating obstruction to one or other inflow or outflow tract, the commonest being the outflow tract of the left ventricle. In the first type systolic murmurs are common, are attributable to atrio-ventricular valve incompetence, and are pan-systolic. In the second type murmurs are equivocal or trivial and may usually be neglected. In the third type the murmurs will vary according to the site of obstruction to blood flow, but in the majority of cases the murmurs are loud and of ejection type.

The presentation with congestive heart failure and a large heart is usually seen in patients in whom the myocardium is extensively involved and becomes flabby and the heart dilated. The presentation with constriction is often found to have associated endocardial and pericardial involvement, and, in addition, a stiff, inelastic myocardium which resists relaxation in diastole, thus simulating constrictive pericarditis. We have termed this type "constrictive cardiomyopathy."

The three groups have been described clinically and the results of special investigations mentioned. Illustrative case histories have been included, as have the results of pathological studies where available. It is suggested that awareness of the types of clinical presentation should facilitate diagnosis, and when this becomes more accurate should lead to valuable clues to the discovery of the cause of many cases of cardiomyopathy.

We are grateful to the physicians of Hammersmith Hospital for permission to study their cases, and the

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REFERENCES

Bercu, B. A., Diettert, G. A., Danforth, W. H., Pund, E. E., jun., Ahlvin, R. C., and Belliveau, R. R. (1958). *Amer. J. Med.*, **25**, 814.
Björk, V. O. (1960). Personal communication.
Brachfeld, N., and Gorlin, R. (1959). *Medicine (Baltimore)*, **38**, 415.
Brent, L. B., Aburano, A., Fisher, D. L., Moran, T. J., Myers, J. D., and Taylor, W. J. (1960). *Circulation*, **21**, 167.
Brigden, W. (1957). *Lancet*, **2**, 1179, 1243.
Brock, R. (1957). *Guy's Hosp. Rep.*, **106**, 221.
—— (1959). Ibid., **108**, 126.
Davies, J. N. P. (1960). *Amer. Heart J.*, **59**, 600.
Goodwin, J. F., Hollman, A., Cleland, W. P., and Teare, D. (1960). *Brit. Heart J.*, **22**, 403.
Hetzel, P. S., Wood, E. H., and Burchell, H. B. (1953). *Proc. Mayo Clin.*, **28**, 107.
Hollman, A., Goodwin, J. F., Teare, D., and Renwick, J. W. (1960). *Brit. Heart J.*, **22**, 449.
Morrow, A. G., and Braunwald, E. (1959). *Circulation*, **20**, 181.
Nye, R. E., jun., Lovejoy, F. W., jun., and Yu, P. N. (1957). Ibid., **16**, 332.
Robin, E. D., and Burwell, C. S. (1957). Ibid., **16**, 730.
Soulié, P., Degeorges, M., Joly, F., Caramanion, M., and Carlotti, J. (1959). *Arch. Mal. Cœur*, **52**, 1002.
Teare, D. (1958). *Brit. Heart J.*, **20**, 1.

EXTENT AND PERMANENCE OF DENERVATION PRODUCED BY LUMBAR SYMPATHECTOMY

A QUANTITATIVE INVESTIGATION OF ITS EFFECTS ON SUDOMOTOR ACTIVITY

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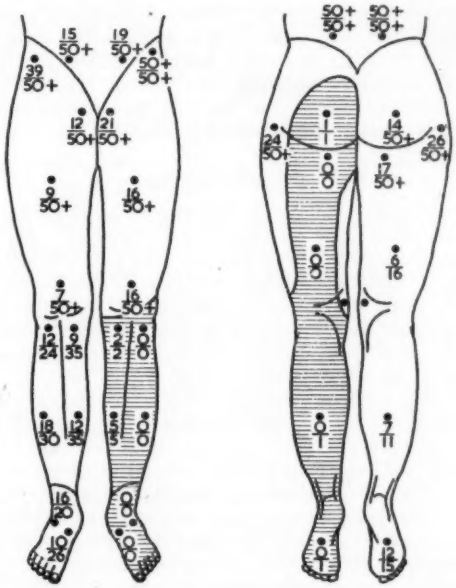
Is the denervation produced by lumbar sympathectomy permanent? This is a controversial topic of obvious practical importance. This paper presents the results of a quantitative investigation into the early and late effects of operation on sudomotor activity, thermoregulatory sweating being a most sensitive index of recovery of sympathetic function. The very different results obtained in the proximal and distal dermatomes of the limb are illustrated, and their mechanism is discussed.

Sweating was determined by measurement of the electrical conductivity of the skin (Richter, 1929). Dry, non-sweating skin is a poor conductor of electricity, while damp sweating skin is a good conductor. As sweating depends on sympathetic sudomotor activity the skin-conductivity measurements can be used to determine the extent of residual sympathetic activity after operation.

Quantitative Sudomotor Test

Nineteen standard points, sited with due regard to the dermatomes, were marked with ink on each of the lower limbs (Fig. 1). The patient then lay on a couch for 20 minutes with the whole of the lower limbs exposed at a laboratory temperature of 22° C. Thereafter, the electrical conductivity of the skin was measured at each of the marked points, using a commercially made skin-conductivity meter (Light Laboratories). An electrical heat cage was then placed over the trunk and face, and body-heating applied for 20 minutes or longer, till the patient was sweating profusely and his oral temperature had risen by at least 0.3° F. (0.17° C.). It is essential for the test that the stimulus to sudomotor activity is maximal. The skin conductivity was again measured at each of the 19 points. The examining electrode was then moved slowly up the limb from the toes towards the trunk until a sudden increase in conductivity occurred. This point, whose position was always quite precise, was marked, and indicated the junction of



LIMB	TOTAL CONDUCTIVITY IN MICRO-AMPS WITHIN THE SHADED AREA		CONDUCTIVITY [INCREASE IN MICRO-AMPS]
	BEFORE HEATING	AFTER HEATING	
SYMPATHECTOMIZED	8	10	2
NORMAL	133	312+	179+

FIG. 1.—A typical quantitative sudomotor test (see text). The current in microamperes at each of the points within the "denervated" (shaded) area is totalled before and after vigorous body-heating. A similar calculation is made within the corresponding area of the non-sympathectomized limb. The increase in conductivity after heating is a measure of sympathetic sudomotor activity.

normally innervated and denervated skin. By moving the electrode up the limb a number of times the points obtained could be linked up round the limb as a line separating the innervated and denervated parts.

The sudomotor test thus yielded information of two kinds: firstly, on the persisting area of partial or complete sympathetic sudomotor denervation below the line drawn round the limb; and, secondly, on the amount of sweating occurring before and after body-heating at a number of fixed points on the skin within this area. The sum of the readings in microamperes at each of the fixed points below the line of denervation gives a measure of sweating within this area. Comparison of sweating in corresponding areas of the sympathectomized and non-sympathectomized limbs

before and after body-heating indicates the extent of sudomotor recovery.

A typical sudomotor test result is illustrated in Fig. 1, and it shows well the method of calculation by which a quantitative measure of sweating is obtained. The patient had had a unilateral sympathectomy two years previously. Even before body-heating the difference in skin conductivity in the two limbs is striking, a total of only 8 μA being recorded within the "denervated" area of the sympathectomized limb, while 133 μA was recorded within the corresponding area of the non-sympathectomized limb. After body-heating, conductivity increased by only 2 μA in the operated limb, but by 179+ μA in the normal limb. (The microammeter of the apparatus measured only up to 50 μA, and when the skin resistance was so low that the current exceeded this the reading was recorded as 50+.)

Clinical Material

Sudomotor activity was investigated in 77 patients, in whom there were 98 sympathectomized and 56 non-sympathectomized lower limbs. The latter, in patients with a unilateral sympathectomy, formed a control group. The early changes resulting from operation were investigated in a number of patients by tests carried out at intervals up to one year after operation. The long-term effects were investigated in 75 patients by tests carried out between one and seven years after operation.

To enable the cutaneous extent of denervation to be correlated with the vertebral level at which the sympathetic chain had been divided, silver clips were placed on the chain at operation just above the highest and below the lowest ganglion removed, and whole-spine radiographs were taken post-operatively. All the operations were performed by me or by one other surgeon, so that the operative technique was fairly uniform.

The area of sudomotor denervation produced by operation is discussed first, and then the evidence of partial recovery of sudomotor activity within this area.

Area of Cutaneous Denervation Produced by Operation

In spite of the fact that the second and lower lumbar ganglia, if not the first, had certainly been removed in all patients, the resulting areas of persisting sudomotor denervation in the 98 limbs, when tested between one and seven years after operation, indicated an apparently

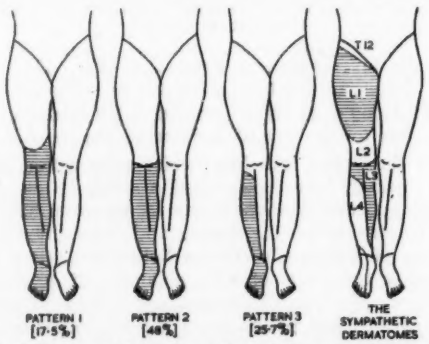


FIG. 2.—The three main patterns of persisting sudomotor denervation present in 98 limbs one to seven years after lumbar sympathectomy, compared with the areas of the sensory and sympathetic dermatomes.

lower level of sympathectomy in them all. The line separating normally sweating from denervated skin lay, in the majority of the limbs, at one or other of three main levels, thus indicating three principal patterns or areas of persisting denervation, partial or complete, best seen on the anterior aspect of the limb (Fig. 2). In pattern 1 (17.5% of the limbs) the upper limit of denervation anteriorly was marked by a transverse or

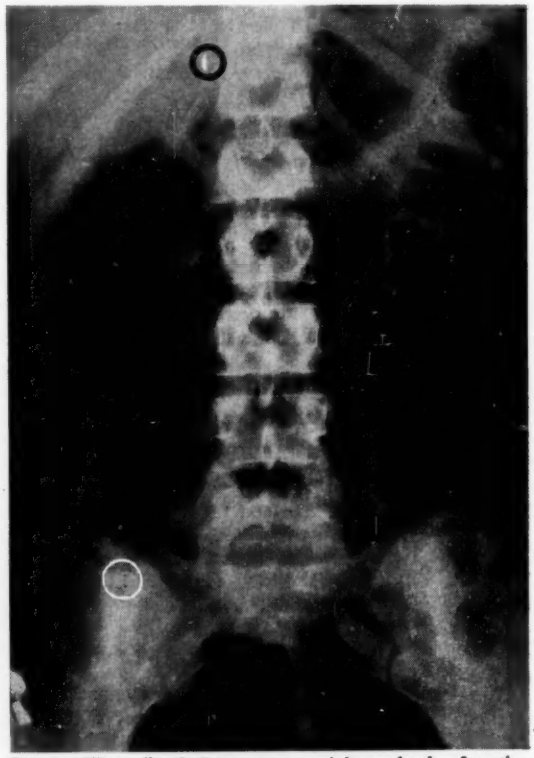


FIG. 3.—Silver clips indicate upper and lower levels of section of sympathetic chain in relation to vertebral bodies. (Case 1.)

obliquely placed line lying somewhere in the lower third of the thigh. In only four patients, included in this group, did the upper limit of denervation lie above the lower third of the thigh. In pattern 2 (48%) the line lay transversely at the level of the knee-joint. In pattern 3 (27.5%) the upper limit of denervation was marked by a line passing from the lateral aspect of the knee down the subcutaneous border of the tibia to the region of the medial malleolus. In addition to these three main patterns of denervation, exhibited by 91% of the limbs, five limbs showed a pattern of denervation between 1 and 2, one limb was denervated only to the level of the ankle anteriorly, while one limb sweated so profusely all over that no area of denervation could be plotted.

When the three main areas of denervation are compared (Fig. 2) with the areas of the sensory and sympathetic dermatomes of Foerster and of Richter and Woodruff (1945), it is seen that the pattern 3 area of denervation corresponds only to a denervation of the fourth lumbar dermatome and below, pattern 2 to a denervation of the third lumbar dermatome and below, and pattern 1 to a denervation of the second lumbar dermatome and below. Of especial interest was

the fact that in only 4 of the 98 limbs did the area of denervation encroach on the first lumbar dermatome.

This anomaly between the segmental level of section of the sympathetic chain and the resulting area of sudomotor denervation is now well recognized, "escape" areas of persistent sweating in the last thoracic and upper one or more lumbar dermatomes originally having been observed after thoracolumbar sympathectomy (Ray and Console, 1948).

It is of some interest to investigate the changes in sudomotor activity within these upper lumbar dermatomes, which apparently are rarely denervated, at intervals after lumbar sympathectomy. The results in a typical patient are illustrated in Figs. 3 and 4. The upper silver clip (Fig. 3) indicates that the sympathetic chain was sectioned at the level of the upper border of the last thoracic vertebra, suggesting that the last thoracic ganglion was probably removed. Eleven days after operation the sudomotor test did in fact show a pattern of denervation extending into the lower abdomen, the area of the last thoracic dermatome (Fig. 4). However, two months after operation apparently normal sweating was found in the last thoracic and much of the first lumbar dermatome, while five months after operation the area of denervation extended only just above the knee, all the first lumbar dermatome now sweating freely. One year after operation the area of sudomotor denervation was unchanged.

In Table I are set out the results of similar tests in 11 patients, and certain conclusions can be drawn from them. (1) Even though the first lumbar ganglion is certainly removed, the first one, two, or three lumbar dermatomes later recover sweating. (2) The area of denervation produced corresponds well to the segmental level of sympathectomy only in the early post-operative period. (3) Recovery of sweating in these lower thoracic and upper lumbar dermatomes is not immediate, however, there being a variable delay. (4) Recovery is often as complete as it will be by eight weeks, and there is never any marked change between the test at about five months and a later test at one year. Recovery thus apparently goes so far and then stops. (5) Recovery seems to take place dermatome by dermatome from above downwards. (6) A "high" sympathectomy may produce a smaller final area of denervation than a lower one. (7) Within the areas of recovery sweating appeared to be normal as judged by skin-conductivity measurements. (8) The lumbar sudomotor dermatomes appear to correspond fairly well in position with the sensory dermatomes.

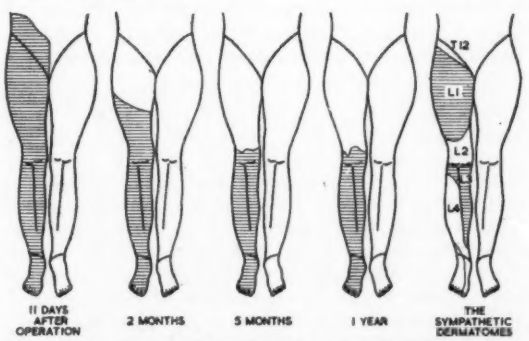


FIG. 4.—Changing area of sudomotor denervation after lumbar sympathectomy. (Case 1.)

Reason for Recovery of Sweating in Upper Part of Limb

There seems no doubt that the reason for the recovery of sweating in the last thoracic and upper lumbar dermatomes is due to the presence of residual sympathetic-nerve pathways which escaped damage at operation. These pathways, which pass via so-called intermediate ganglia lying outside the paravertebral sympathetic chain, have aroused much recent anatomical interest, fully reviewed by Boyd (1957). While the presence of the intermediate ganglia has long been known to anatomists, their functional significance was unrealized till Ray and Console (1948) attributed the escape areas of sudomotor denervation seen after thoracolumbar sympathectomy to their activity.

TABLE I.—*Area of Sudomotor Denervation Present on Anterior Aspect of Leg at Intervals After Lumbar Sympathectomy of Varying Extent*

Case No.	Vertebral Level of Upper Section of Sympathetic Chain	Highest Dermatome Showing Sudomotor Denervation at Intervals after Operation			
		1st Test	2nd Test	3rd Test	4th Test
1	Upper border T 12	11 days T 12	8½ weeks L 1/2	22 weeks L 2	1 year L 2
2	Upper border T 12	7 days T 12	11 weeks L 3		1 year L 3
3	Middle of T 12	4 days T 12	6 weeks L 4	17 weeks L 4	1 year L 4
4	Lower border T 12	12 days T 12	5 weeks L 3	16 weeks L 3	1 year L 3
5	Lower border T 12	6 days L 1	6 weeks L 3		
6	Junction of T 12/L 1	10 days L 1	5 weeks L 1	16 weeks L 3	1 year L 3
7	Junction of T 12/L 1	8 days L 1	5 weeks L 3		
8	Upper border L 1	4 days L 1	6 weeks L 1/2	17 weeks L 2/3	1 year L 3
9		7 days L 1	9 weeks L 1/2	20 weeks L 1/2	1 year L 1/2
10	Middle of L 1	8 days L 2	8 weeks L 3	20 weeks L 3	1 year L 3
11	Upper border L 2	7 days L 2	7 weeks L 3		

Note.—Where the dermatome is given as L 1/2, for example, this indicates that the upper limit of denervation was very low on the L 1 dermatome, almost down to the L 2 area.

There are good grounds for believing that residual pathways rather than regeneration, as ordinarily understood, are responsible for the early segmental return of sudomotor activity in the lower limb after lumbar sympathectomy. (1) If chance regeneration was occurring, then recovery of sweating would certainly be scattered, and incomplete in any dermatome. (2) Neither would recovery cease so abruptly when a certain segmental level of reinnervation had been reached. (3) "High" sympathectomy may result in a lower final level of denervation than a lower sympathectomy, suggesting that the main factor determining the final level of denervation is the number of lumbar segments having residual pathways. (4) Also, as strong evidence for bilaterally symmetrical residual pathways, was the finding that in 20 patients who had had a bilateral sympathectomy, with an interval of up to several years between operations, the final area of denervation was the same in both limbs in 17. It is most unlikely that exactly the same amount of sympathetic chain was removed on the two sides of each of these patients. If chance regeneration was occurring, then the likelihood of a similar final pattern of denervation in the two limbs would be small.

The number of segments in which residual pathways are present varies in individuals, though they seem almost invariably to occur in the last thoracic and first lumbar segments, and often in the second and third lumbar segments also. This is well illustrated by the findings in the 98 limbs (Fig. 2). Residual pathways

are rarely present in segments lower than the third lumbar. As would be expected, they are bilaterally similar.

Mechanism by Which Residual Pathways Restore Sympathetic Innervation

While it might be that the residual pathways by themselves restore normal innervation, it seems likely that the process of reinnervation is a little more complicated. Of particular interest is the variable delay of several weeks to several months before recovery is complete. It is difficult to explain this delay in function in pathways which are already anatomically complete.

One possible explanation of a temporary delay in function in the residual pathways after operation is that degeneration in the post-ganglionic fibres of the extirpated paravertebral ganglia interferes temporarily with conduction in the post-ganglionic fibres of the intact intermediate ganglia running with them in the peripheral nerves. A somewhat similar phenomenon occurs in relation to taste, for example. If the semilunar ganglion of the fifth cranial nerve is destroyed the sense of taste is temporarily lost over the anterior two-thirds of the tongue, but is recovered after about two weeks (Wright, 1952). The fibres of the chorda tympani, responsible for carrying the sense of taste from this area, do not traverse the semilunar ganglion but pass as passengers in the lingual nerve, which has its cell bodies in this ganglion. When the fibres of the lingual nerve degenerate after damage to the ganglion, conduction is temporarily interfered with in the chorda tympani. This explanation of delay in functional activity in the residual pathways might also fit with the recovery of sweating in the lower limb dermatome by dermatome distally, degeneration going on for longer in the longer pathways and hence interfering for a greater period with conduction in the residual sympathetic fibres of these dermatomes.

However, while temporary interference with conduction in the residual pathways may well be the explanation of a delay in the beginning of recovery lasting up to two weeks, it is less easy to ascribe to it the longer delays which sometimes occur before recovery has reached its final extent. There is, in fact, a more likely explanation of the later complete recovery of innervation in the dermatomes supplied by the residual pathways.

Murray and Thompson (1957) demonstrated the occurrence of profuse collateral sprouting from the remaining fibres after partial section of a sympathetic-nerve trunk. These collateral sprouts grow down the distal part of the divided fibres to give complete reinnervation. It seems most probable that such sprouting occurs from the post-ganglionic fibres of the undamaged intermediate ganglia soon after sympathectomy, the sprouts establishing connexion with the decentralized post-ganglionic fibres of the excised paravertebral ganglion of the segment. In this way complete recovery of sweating occurs after a variable delay in every segment having residual pathways, but only in these segments, the most proximal dermatome concerned, as its pathway is shortest, recovering sweating first.

Clinical Implications of Recovery of Sudomotor Innervation in the Thigh

It has often been stated that removal of the first lumbar ganglion is essential to ensure denervation of the collateral vessels in the thigh, the common site of arterial occlusions in obliterative vascular disease (Ratcliffe and Jepson, 1950). However, if the usual recovery of sympathetic sudomotor activity in the thigh is associated with a similar recovery of sympathetic vasomotor activity, it seems pointless to extend the dissection at sympathectomy to include the first lumbar ganglion. There is, in fact, no definite evidence that vasomotor recovery in the thigh does parallel sudomotor recovery, but Dornhorst and Sharpey-Schafer (1951) did find that lumbar sympathectomy produced only a transient reduction in collateral resistance round femoral-artery occlusions, resistance being back to its pre-operative level within about two weeks. It seems not unreasonable to suppose that if collateral sprouting leads to restoration of the sudomotor pathway it will equally lead to restoration of the vasomotor.

If no lasting vasomotor denervation in the thigh follows removal of the first lumbar ganglion, then leaving it *in situ* at operation may reduce the incidence of post-sympathectomy neuralgia in the thigh (De Bakey, Crawford, Cooley, and Morris, 1958) and the more nebulous risk of male sexual dysfunction after bilateral operations.

So much for the activity of the residual nerve pathways in the recovery of sudomotor activity in the upper lumbar segments after sympathectomy: the evidence for the occurrence of some partial recovery of sudomotor activity within the apparently denervated more distal parts of the limb is now presented.

Evidence of Partial Recovery of Sudomotor Activity Within Apparently Denervated Distal Parts of Limb

The sudomotor test was applied in 97 of the limbs sympathectomized between one and seven years previously. Of these limbs, 82% showed some increase in conductivity after body-heating, a figure which compares closely with Haxton's (1947) 83%, and might support the view that the lower limb is not immune to sympathetic recovery after the lumbar operation. However, the present quantitative investigation (Table II) shows that, even though most of the limbs showed some recovery of sweating, the extent of the recovery was very small, probably in most limbs being insignificant.

TABLE II.—*Results of Skin-conductivity Test in 76 Patients*

Type of Limb	No. of Limbs	Mean Conductivity before Heating (μA)	Mean Increase in Conductivity after Heating (μA)
Sympathectomized	97	7·9 (S.E. 0·97)	7·4 (S.E. 1·13)
Non-sympathectomized	53	58·2 (S.E. 6·33)	166·8 (S.E. 14·15)

Note.—The difference between the means in column three is significant at the 0·1% level, as is the difference between the means in column four.

For example, even before body-heating there was a highly significant difference (at the 0.1% level) in the mean conductivity of the sympathectomized and non-sympathectomized limbs—7.9 and 58.2 μA respectively—while after body-heating the mean increase in conductivity was only 7.4 μA in the sympathectomized limbs compared with 166.8+ μA in the control limbs, this difference again being highly significant (at the 0.1% level). These figures can be further broken down: the increase, if any, in conductivity on body-heating in the sympathectomized limbs was less than 5 μA in 51 limbs, between 5 and 10 μA in 24 limbs, and in only one limb did it exceed 34 μA. These findings are to be

contrasted with those for the control limbs, in which the smallest increase was 34 μA and the largest 515+ μA, while in over two-thirds of these limbs it exceeded 100 μA. In short, the mean increase in conductivity in the sympathectomized limbs after body-heating amounted to less than 5% of that in the normally innervated control limbs.

Mechanism of Scattered Peripheral Recovery of Sudomotor Activity

The mechanism by which this scattered return of sudomotor activity in the more distal parts of the leg occurs cannot at first sight so readily be explained by activity of the residual pathways, as these apparently are arranged on a strictly segmental basis and are present only in the upper dermatomes of the limb. However, it is likely that a few collateral sprouts from post-ganglionic fibres of the undamaged intermediate ganglia make chance contact with decentralized post-ganglionic fibres of the extirpated paravertebral ganglia of lower segments. Such scattered peripheral recovery of sudomotor activity as results may therefore be regarded as purely accidental. In favour of this view is the fact that there is seldom any significant degree

TABLE III.—*Effect of Time on Partial Peripheral Recovery of Sudomotor Activity in Sympathectomized Limbs*

Interval between Operation and Testing	No. of Limbs	Mean Skin-Conductivity Increase (μA)	S.E. of Mean Conductivity Increase (μA)
2 to 7 years	51	6·2	1·15
1 ,, 2 ,, ...	46	8·6	2·01

Note.—There is no significant difference in the mean conductivity increase in the two groups of limbs.

of recovery, and that this process of recovery is not a progressive one. For example, the mean increase in conductivity on body-heating in those limbs tested between two and seven years after operation was not significantly different from that in limbs tested between one and two years after operation (Table III).

The findings suggest that, apart from the effects of scattered accidental rerouting, lasting sympathetic denervation in the distal dermatomes of the lower limb is produced by lumbar sympathectomy.

Correlation Between Evidence of Recovery of Vasomotor and of Sudomotor Activity

In conclusion, it is of interest to note the "curious fact" reported by Barcroft and Hamilton (1948a, 1948b), amongst others, that after cervico-dorsal sympathectomy the sudomotor reflex, but not the vasomotor, may return in the hand. In the present work such a correlation between vasomotor and sudomotor recovery was sought in 26 lower limbs sympathectomized between one and seven years previously for non-obliterative disease. Blood-flows were measured by venous occlusion plethysmography before and after body-heating (Gillespie, 1960), and the sudomotor test was carried out as described above.

The results (Table IV) confirm those obtained in the upper limb—namely, that some sudomotor activity may be present even if vasomotor activity is not demonstrable. Slight sudomotor activity was present in 12 limbs in which vasomotor activity apparently was not, while the reverse occurred in only two limbs. This illustrates the greater sensitivity of the skin-conductivity test in detecting the presence of minimal sympathetic activity post-operatively.

TABLE IV.—*Comparison of Recovery of Sympathetic Sudomotor and Vasomotor Activity in 26 Lower Limbs Sympathectomized for Non-obliterative Vascular Disease Between One and Seven Years Previously*

	Sudomotor but Not Vasomotor	Vasomotor but Not Sudomotor	Sudomotor and Vasomotor	Neither Sudomotor nor Vasomotor
No. of legs ..	12	2	6	6

Summary

The effects of lumbar sympathectomy on sudomotor activity in the lower limb have been investigated in a quantitative manner in 77 patients.

Complete recovery of sympathetic sudomotor innervation is the rule in the last thoracic and first lumbar dermatomes, and is common in the second and third lumbar dermatomes. This recovery is usually as complete as it will be within a few weeks or months after operation. The evidence that it is almost certainly due to the activity of residual nerve pathways is discussed. The practical implication of this recovery is that nothing is gained by removing the lower thoracic and upper lumbar ganglia at operation.

Lumbar sympathectomy, apart from the effects of accidental rerouting, produces lasting sympathetic denervation of the more distal dermatomes. The amount of sweating in response to body-heating averages less than 5% of normal in these dermatomes.

Slight recovery of sudomotor activity is more often demonstrable than recovery of vasomotor activity in sympathectomized lower limbs.

I thank Professor D. M. Douglas for the interest he has taken in this work, and Professor A. C. Dornhorst for helpful criticism of the presentation. It is also a pleasure to record my appreciation of the willing technical assistance given by Mr. William Muir. Miss B. J. Kinsley kindly undertook the statistical evaluation of the results. The work was undertaken with the assistance of a grant from the Scottish Hospital Endowment Research Trust, and was carried out in the research laboratories of the Department of Clinical Surgery, Royal Infirmary, Dundee.

REFERENCES

Barcroft, H., and Hamilton, G. T. C. (1948a). *Lancet*, **1**, 441.
—— —— (1948b). Ibid., **2**, 770.
Boyd, J. D. (1957). *Brit. med. Bull.*, **13**, 207.
De Bakey, M. E., Crawford, E. S., Cooley, D. A., and Morris, G. C., jun. (1958). *Ann. Surg.*, **148**, 306.
Dornhorst, A. C., and Sharpey-Schafer, E. P. (1951). *Clin. Sci.*, **10**, 371.
Gillespie, J. A. (1960). *Lancet*, **1**, 891.
Haxton, H. A. (1947). *Brit. J. Surg.*, **35**, 69.
Murray, J. G., and Thompson, J. W. (1957). *J. Physiol. (Lond.)*, **135**, 133.
Ratcliffe, A. H., and Jepson, R. P. (1950). *J. Neurosurg.*, **7**, 97.
Ray, B. S., and Console, A. D. (1948). Ibid., **5**, 23.
Richter, C. P. (1929). *Bull. Johns Hopk. Hosp.*, **45**, 56.
—— and Woodruff, B. G. (1945). *J. Neurophysiol.*, **8**, 323.
Wright, S. (1952). *Applied Physiology*, 9th ed., p. 581. Oxford Medical Publ., London.

"In 1949 Newfoundland became the tenth province of Canada and came under Canada's immigration and taxation laws—with a corresponding increase in Federal money grants for social services. In the last ten years standards of health and welfare have been raised enormously. In "the hungry thirties," deficiency diseases and frank starvation were common in the fishing villages around the coasts, while tuberculosis was a great problem. These conditions are now comparatively rare. The tuberculosis mortality rate is nearly as low as Canada's and the sanatoria are half empty. Adequate medical care is available in all the large centres, although some of the outports have no doctors, and medical care is given through nursing stations." (Dr. J. S. Harley, Newfoundland, in *Chest and Heart Bulletin*, December, 1960.)

EFFECTS OF SPLENECTOMY ON RED-CELL PRODUCTION IN MYELOFIBROSIS

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It has often been stated that in myelofibrosis the spleen becomes an important site of extramedullary erythropoiesis, and that splenectomy or splenic irradiation is harmful (Donhauser, 1908; Hickling, 1937; Jackson, Parker, and Lemon, 1940; Reich and Rumsey, 1942; *Lancet*, 1949; Sanneman, McIlvanie, and Beard, 1950; Learmonth, 1951). However, successful splenectomy has been reported by several authors, some of whom state that there was no evidence of diminished erythropoiesis after splenectomy (Edwards, 1951; Claman and Collier, 1952; Franks and Richardson, 1952; Green, Conley, Ashburn, and Peters, 1953; Hutt, Pinniger, and Wetherley-Mein, 1953; Panels in Therapy, 1955; Videbaek, 1956; Shinton, 1957; Andreasen, 1958).

Despite these observations the view that splenectomy is contraindicated is still widely held, and a recent review stated: "The treatment of myelosclerosis is based on the recognition that the haemopoiesis in the spleen is responsible for an increasing proportion of the patient's supply of blood cells. Splenectomy is therefore not proper treatment" (*Brit. med. J.*, 1960). We report two cases of myelofibrosis in which the course and findings after splenectomy throw doubt on the universal validity of this last conclusion. Evidence was obtained that in these two cases splenectomy was followed by increased red-cell production.

Methods

Plasma Iron.—The method of Bothwell and Mallett (1955) was used.

Isotope Techniques

^{59}Fe Utilization and Surface Counting Pattern.—10 μc of $^{59}FeCl_3$ buffered with sodium citrate was injected intravenously. A ^{59}Fe surface counting pattern was then obtained, using a directional scintillation counter, and counts were made over praecordium, sacrum, liver and spleen. The counting rate over the praecordium was taken to represent blood ^{59}Fe activity and that over the sacrum to represent marrow ^{59}Fe activity. The counting rates over each organ were plotted arithmetically against the time after the injection of ^{59}Fe plotted logarithmically (Fig. 1). The technique used is described in detail by Wetherley-Mein, Hutt, Langmead, and Hill (1956). Blood samples were taken and the percentage of the administered dose of ^{59}Fe which appeared in the circulating red-cell volume was calculated from the activity per ml. of blood and the blood volume. This percentage is referred to as the ^{59}Fe utilization. Normal subjects have a ^{59}Fe utilization of at least 70% by the seventh day.

^{51}Cr Red-cell Survival.—20 ml. of the patient's blood was withdrawn into heparin, centrifuged, and the supernatant plasma removed. To the red cells was added 100 μc of ^{51}Cr as $Na_2{}^{51}CrO_4$, and the mixture was allowed to stand at room temperature for 30 minutes. Excess ^{51}Cr was removed by washing in normal saline, and the tagged red cells were reinjected

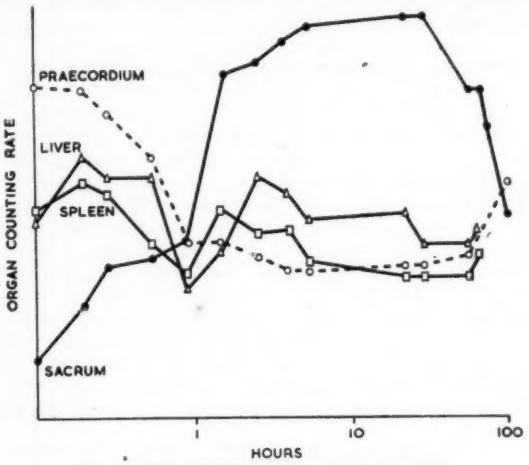

FIG. 1.—Normal ^{59}Fe surface-counting pattern.

into the patient. The total red-cell volume was calculated from the dilution of these cells in the circulation at 20 minutes. The apparent ^{51}Cr red-cell survival was calculated from the decline in specific activity of ^{51}Cr per ml. of whole blood.

Since the clinical situation before splenectomy precluded a long-term ^{51}Cr study, a short-term ^{51}Cr technique over 10 days was used and a comparable study performed after operation. The brevity of these studies did not allow an estimate of mean red-cell life to be made with any accuracy, and $T\frac{1}{2}$ ^{51}Cr could be determined only after considerable extrapolation. The values obtained for ^{51}Cr activity on successive days were therefore plotted on semi-logarithmic paper and the best-fitting straight line through the points was drawn. From the slope of this was calculated the rate of ^{51}Cr loss from the circulation (expressed as percentage loss of ^{51}Cr per day). No correction was made for ^{51}Cr elution from intact red cells.

We have studied with this short ^{51}Cr technique 10 normal subjects and 11 patients having normal ^{51}Cr red-cell survival curves (Jones, Wetherley-Mein, Ingram, and Langmead, 1960). From an analysis of the results it appears that only 1 in 20 normal subjects would be expected to show rates of ^{51}Cr loss greater than 5.1% a day over the first 10 days of the study, and rates exceeding 5.1% a day may therefore be regarded as abnormal. It is not legitimate to infer normal red-cell survival from rates of ^{51}Cr loss less than 5.1% a day, but it may then be inferred that haemolysis is not contributing greatly to an anaemia.

Case 1

Summary of Haematological Findings (Fig. 2).—This patient maintained a haemoglobin level of between 8.3 and 12 g./100 ml. for five years after the diagnosis of myelofibrosis. The haemoglobin level then fell to 5 g./100 ml. and could hardly be raised by transfusion. Isotope studies showed greatly reduced red-cell production and there was evidence of shortened red-cell life. Prednisone therapy had

no effect on the haemoglobin level. Splenectomy was therefore performed and the haemoglobin was subsequently maintained at about 11 g./100 ml. without further therapy. Isotope studies now showed a very considerable increase in red-cell production compared with the pre-operative findings. There was now no evidence of shortened red-cell life.

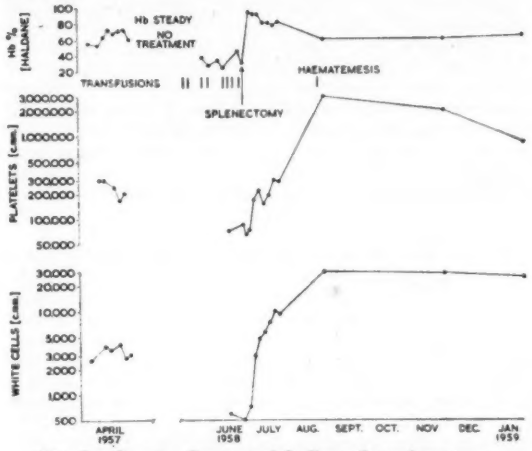

FIG. 2.—Case 1. Course and findings after splenectomy.

History and Findings Before Splenectomy

In 1953 myelofibrosis was diagnosed in this 57-year-old man on the basis of splenomegaly, leuco-erythroblastic anaemia, dry sternal puncture, and the histology of a rib biopsy taken at another hospital.

He was first admitted to St. Thomas's Hospital in November, 1955, when investigations showed: Hb, 12 g./100 ml.; P.C.V., 39%; M.C.V., 118 cubic microns; M.C.H.C., 30.75%; reticulocytes, 3.1%; direct Coombs test negative; W.B.C., 4,500/c.mm. (segmented neutrophils 70%, lymphocytes 20%, monocytes 6%, metamyelocytes 3%, neutrophil myelocytes 1%); platelets, 368,000/c.mm. Microscopy of the original rib-biopsy material showed a considerable increase in reticulin fibrils throughout the marrow with, in some areas, extensive collagen formation. There was appreciable haemopoietic activity in the less densely fibrotic areas, the predominant cells being mature granulocytes, although erythropoietic foci could be identified. Megakaryocyte-like giant cells were enormously increased in numbers throughout. There was no evidence of active bone formation. A ^{59}Fe study was performed, and this suggested a partial failure of red-cell production (see Results, Case 1 (a)).

The patient was next admitted in April, 1957, on account of abdominal discomfort due to enlargement of the spleen, which extended to the left iliac fossa. Investigations: Hb, 8.3 g./100 ml.; W.B.C., 2,600/c.mm. (neutrophils 64%, lymphocytes 33%, monocytes 2%, eosinophils 1%); platelets, 198,000/c.mm. After a course of busulphan the spleen diminished slightly in size.

In May, 1958, the patient became increasingly tired and breathless on exertion. On his admission to another hospital the haemoglobin was found to be 4.9 g./100 ml. and a blood transfusion was given. A month later on readmission to St. Thomas's Hospital he was found to be extremely pale but not jaundiced. There was oedema of ankles and sacrum, and the jugular venous pressure was raised 1 in. (2.5 cm.). A soft systolic murmur was audible over the whole praecordium, but the heart was not enlarged radiologically. The spleen was grossly enlarged, reaching to the left iliac crest and extending across the midline into the right iliac fossa: it was very tender. The liver was palpable 1 in. (2.5 cm.) below the right costal margin. No enlarged lymph nodes were detected. Investigations: Hb, 3.5 g./100 ml.; P.C.V., 12%; reticulocytes, 5%; direct Coombs test negative; W.B.C., 600/c.mm. (neutrophils 73%, lymphocytes 23%, plasma cells 4%); platelets, 70,000/c.mm.; plasma iron, 246 μg./100 ml.; serum bilirubin, 0.65 mg./100 ml. The stools contained no occult blood.

Treatment with prednisone was started and ^{59}Fe and ^{51}Cr studies were begun. The ^{59}Fe study showed an almost complete failure of erythropoiesis (see Results, Case 1 (b)). ^{51}Cr-survival studies were interrupted by blood transfusion, but the rate of fall of haemoglobin—6% (Haldane) a day in the absence of haemorrhage—indicated considerable haemolysis.

It was now difficult to raise the haemoglobin by transfusion; the patient became critically ill, and splenectomy was undertaken in June as an emergency procedure. The spleen weighed 2,670 g., and microscopy showed disruption of the normal architecture, diffuse proliferation of reticulum cells with collagen formation, and occasional megakaryocyte-like giant cells. Red-cell precursors were abundant and scattered diffusely throughout. Granulocyte precursors were present but less numerous.

Course and Findings After Splenectomy (Fig. 2)

Post-operatively there was a remarkable clinical improvement. The haemoglobin level became steady at 11.1 g./100 ml., the W.B.C. rose rapidly from 700 to 9,000/c.mm. and the platelet count from 68,000 to 300,000. Four weeks later isotope studies showed a striking increase in red-cell production (see Results, Case 1 (c)). Five weeks after operation the patient left hospital.

In August, 1958, a small haematemesis occurred, and he was transfused. At this time the platelet count was 3,200,000/c.mm. and the W.B.C. 28,000/c.mm. He remained well until July, 1959, when he developed pain in the lower thoracic and upper lumbar spine. He became breathless on exertion, and was readmitted in August. The outstanding findings on examination were pallor, and enlargement of the liver, which was now palpable 4 in. (10 cm.) below the right costal margin and contained several prominent lumps, the largest of which was about 7 cm. in diameter. Investigations: Hb, 5.9 g./100 ml.; M.C.H.C., 25%; reticulocytes, 7.2%; direct Coombs test negative; W.B.C. 19,700/c.mm. (neutrophils 86%, lymphocytes 6%, monocytes 1%, eosinophils, 1%, basophils 1%, metamyelocytes 3%, blast cells 2%); 74 normoblasts per 100 white cells; platelets, 888,000/c.mm. Plasma iron 22 μg./100 ml. Tests for occult blood in the stools were positive. A ^{59}Fe surface counting pattern was obtained (see Results, Case 1 (d)). The absolute values, low plasma iron, and the presence of blood in the stools indicated an iron-deficiency anaemia due to gastro-intestinal blood loss.

Chest *x*-ray examination showed a round shadow in the left mid-zone which tomography indicated was situated posteriorly in the left upper lobe. No tubercle bacilli or neoplastic cells were found on examination of the sputum. A provisional diagnosis of carcinoma of the bronchus with liver metastases was made. *X*-ray examination of the painful areas of the spine revealed no evidence of metastases.

Two days after admission the patient had two haematemeses, and was transfused. A barium-meal examination showed a small projection of barium on the lesser curve of the stomach. The patient's general condition deteriorated steadily, and he died on September 9, 1959.

Post-mortem Examination

The bronchus to the apical segment of the left upper lobe was stenosed by tumour. Purulent tracheobronchitis and a small recent pulmonary infarct in the right lower lobe were also noted.

The liver was greatly enlarged and contained many deposits of tumour tissue. The anterior wall of the stomach was adherent to a large liver metastasis, and this had caused tethering of the gastric mucosa. Metastases were also present in the right adrenal gland, the right kidney, parietal peritoneum, retroperitoneal lymph nodes, and right cerebral

hemisphere. No macroscopic evidence of skeletal metastases was found.

Histological examination of the primary neoplasm in the lung and of the metastases revealed a spheroidal-cell carcinoma. Microscopy of the liver showed a slight increase in connective tissue with occasional megakaryocyte-like giant cells but no evidence of extramedullary erythropoiesis.

The marrow was cellular and contained numerous megakaryocyte-like giant cells. Many foci of red-cell precursors were present and granulocyte precursors were diffusely distributed throughout. Increased proliferation of reticulum cells was noted, but collagen formation was slight except in one area adjacent to a small nest of carcinoma cells.

When compared with the histological appearances of the rib biopsy taken in 1953, erythropoietic tissue was much more evident in the post-mortem specimen. The granulopoietic cells contained proportionately greater numbers of immature forms. Megakaryocyte-like giant cells were still present in excess but were less abundant than in the original sections. Reticulum-cell proliferation was less evident in the post-mortem sections and there appeared to be less collagen formation, although it was difficult to be certain about this.

Case 2

Summary of Haematological Findings (Fig. 3).—For one year after a diagnosis of myelofibrosis had been made in this patient, regular blood transfusions were needed to maintain the haemoglobin level. The rate of fall of haemoglobin was about 1% (Haldane) a day, and isotope studies showed greatly reduced red-cell production without increased red-cell destruction. It became progressively more difficult to raise the haemoglobin level by transfusion, and isotope studies then showed a shortened red-cell life. Splenectomy was performed, and after operation the haemoglobin level was maintained at about 12 g./100 ml. without further therapy. Isotope studies now showed a considerable rise in red-cell production and no evidence of shortened red-cell life. The patient later developed obstructive jaundice and died three and a half months after splenectomy. During this latter period the haemoglobin level fell slowly to 10 g./100 ml., and there became steady.

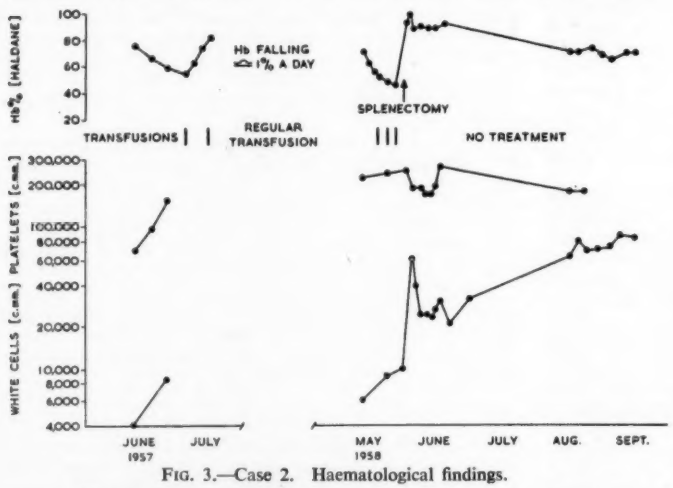

FIG. 3.—Case 2. Haematological findings.

History and Findings Before Splenectomy

In April, 1957, splenomegaly was discovered in this 56-year-old woman at laparotomy performed at another hospital on account of abdominal pain. A post-operative diagnosis of myelofibrosis was made on the basis of a leuco-erythroblastic anaemia and the histology of a rib biopsy taken after a dry sternal puncture.

On the first admission to St. Thomas's Hospital in June, 1957, the spleen reached the left iliac fossa, and anaemia and purpura were noted. The liver was not palpable. Investigations: Hb, 10 g./100 ml.; P.C.V., 36.5%; M.C.H., 31 $\mu\mu$g.; M.C.H.C., 30%; reticulocytes, 3%; 2 normoblasts per 100 white cells; W.B.C., 4,100/c.mm. (segmented neutrophils 61%, lymphocytes 34%, monocytes 3%, eosinophils 2%); platelets, 67,000/c.mm.; direct Coombs test negative; E.S.R., 7 mm. in 1 hour (Westergren). Examination of the original rib-biopsy material showed a considerable increase in reticulin fibrils throughout the marrow, with widespread collagen formation. Granulocyte precursors were evident throughout, but only occasional foci of erythropoietic cells were seen. There was a moderate increase in megakaryocyte-like giant cells. Active bone formation was not observed. ^{59}Fe and ^{51}Cr studies suggested considerably reduced red-cell production with no evidence of increased red-cell destruction (described under Results, Case 2 (a)).

For the next 10 months the haemoglobin level fell about 1% (Haldane) a day, necessitating regular blood transfusion. Increasing difficulty in maintaining the haemoglobin level led to readmission in May, 1958. The spleen was greatly enlarged and reached the right iliac fossa, but the liver was impalpable. Investigations: Hb, 10.4 g./100 ml.; reticulocytes, 6.3%; direct Coombs test negative; W.B.C., 6,200/c.mm. (segmented neutrophils 69%, band neutrophils 3%, neutrophil metamyelocytes 2%, lymphocytes 22%, monocytes 3%, basophils 1%); platelets, 221,000/c.mm. Plasma iron 289 μg./100 ml.

^{59}Fe and ^{51}Cr studies indicated a severe failure of erythropoiesis with evidence of shortened red-cell life (described under Results, Case 2 (b)). The haemoglobin level was now falling about 2% (Haldane) a day, and the reticulocyte count varied between 4.5% and 7.1%.

In view of these findings and the steady deterioration of the patient's condition splenectomy was performed. The spleen weighed 4,490 g. There was loss of the normal architecture with proliferation of reticulum cells and megakaryocyte-like giant cells. Throughout there were numerous foci of red-cell precursors with a more diffuse distribution of granulocyte precursors. A liver biopsy showed considerable proliferation of reticulum cells in the portal tracts. Accumulations of normoblasts, granulocytes, and occasional megakaryocyte-like giant cells were present in the liver sinusoids.

Course and Findings After Splenectomy (Fig. 3)

After splenectomy the haemoglobin level became steady at about 12 g./100 ml. The ^{59}Fe utilization was much higher than before splenectomy, while the ^{51}Cr study now provided no evidence of shortened red-cell survival (see Results, Case 2 (c)). There was a considerable rise in W.B.C. but a slight and short-lived fall in platelet count (Fig. 3). The general condition of the patient was strikingly improved, and she left hospital five weeks after operation.

She remained well for the next two months but then gradually became jaundiced and was readmitted. The liver was now palpable 5 in. (12.5 cm.) below the right costal margin. The urine contained bile and an excess of urobilinogen, but the latter disappeared after two or three weeks. Investigations: serum bilirubin, 3.8 g./100 ml.; thymol turbidity, 2 units; alkaline phosphatase, 232 King–Armstrong units; plasma albumin, 3.1 g./100 ml.; plasma globulin, 2.2 g./100 ml.; serum electrophoresis showed a slight increase in the gamma-globulin fraction; serum cholesterol, 845 mg./100 ml.; serum calcium, 7.7 mg./100 ml.; serum phosphorus, 3.7

mg./100 ml.; prothrombin time, 16 secs. (control, 14 secs.); blood urea, 42 mg./100 ml. On a normal ward diet the stool contained 47 g. of fat a day, and when ^{131}I triolein was given by mouth 71% of the dose appeared in the stools during the next five days (normal 0 to 5%). Thus there was evidence of obstructive jaundice with gross steatorrhoea. Haematological investigations showed: Hb, 10 g./100 ml.; reticulocytes, 2.6%; direct Coombs test negative; W.B.C., 63,000/c.mm. (segmented neutrophils 87%, band neutrophils 1%, lymphocytes 9%, atypical mononuclears 3%); platelets, 157,000/c.mm. A ^{59}Fe study was performed (see Results, Case 2 (d)).

Six weeks later the patient died. During this period there was no further haematological deterioration. Permission for necropsy was not granted.

Results of ^{59}Fe and ^{51}Cr Studies

Case 1

(a) November, 1955.—^{59}Fe utilization, 48% by the seventh day. The ^{59}Fe surface counting pattern obtained is shown in Fig. 4. When compared with the normal pattern (Fig. 1) the major differences are: the rise in counting rate over the sacrum was much reduced; the counting rate over the spleen was initially high and rose to a peak at about four hours.

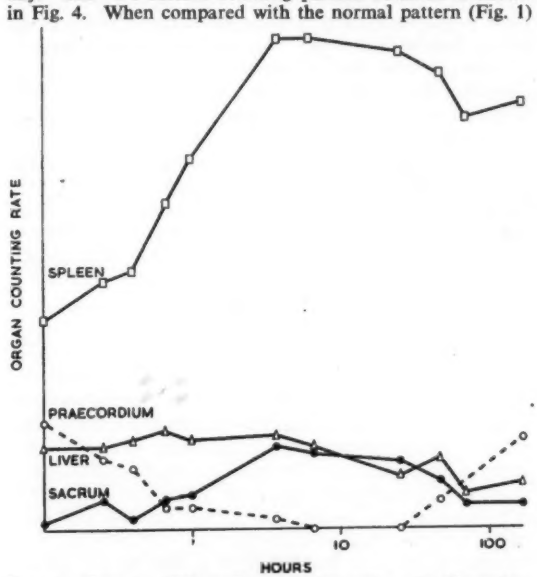

FIG. 4.—Case 1. ^{59}Fe surface-counting pattern in November, 1955 (pre-splenectomy).

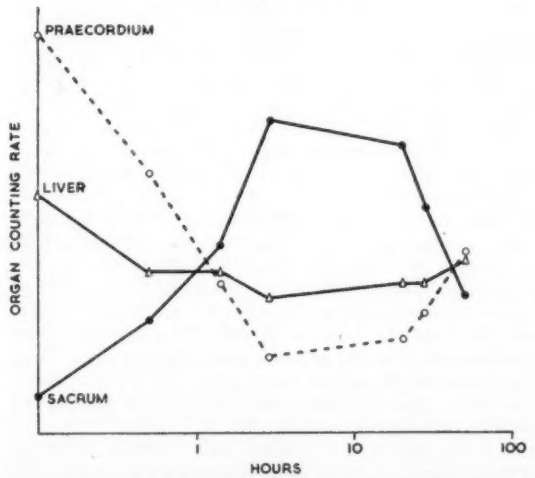

FIG. 5.—Case 1. ^{59}Fe surface-counting pattern in August, 1959 (post-splenectomy).

(b) June, 1958.—^{59}Fe utilization, 5% by the fifth day, when the study was abandoned as transfusion was necessary. The shape of the curve relating ^{59}Fe utilization to time is such that the above measurement would indicate a seventh-day utilization of about 10%. Plasma iron, 246 μg./100 ml. Surface pattern: the rise in counting rate over the sacrum was again much reduced; the counting rate over the spleen was again raised and reached a peak at 72 hours, but this rise was less pronounced than in the previous study; the counting rate over the liver rose slightly during the first 24 hours.

(c) July, 1958 (Post-splenectomy).—Performed at a time when the haemoglobin level had become steady. ^{59}Fe utilization, 91% (the seventh day). Plasma iron, 200 μg./100 ml. Surface pattern, unsatisfactory owing to technical difficulties.

(d) August, 1959.—Surface pattern (Fig. 5) shows a peak in the counting rate over the sacrum of almost normal height and contour. There was no abnormal increase in counting rate over the liver. The study was abandoned (owing to transfusion) before a satisfactory measure of ^{59}Fe utilization could be obtained. Plasma iron, 22 μg./100 ml.

Case 2

(a) June, 1957.—^{59}Fe utilization, 26%. Surface pattern (Fig. 6) shows little rise in counting rate over the sacrum, a high counting rate over the spleen reaching a peak at about six hours, and a raised counting rate over the liver which did not greatly alter. ^{51}Cr red-cell loss, 4% a day.

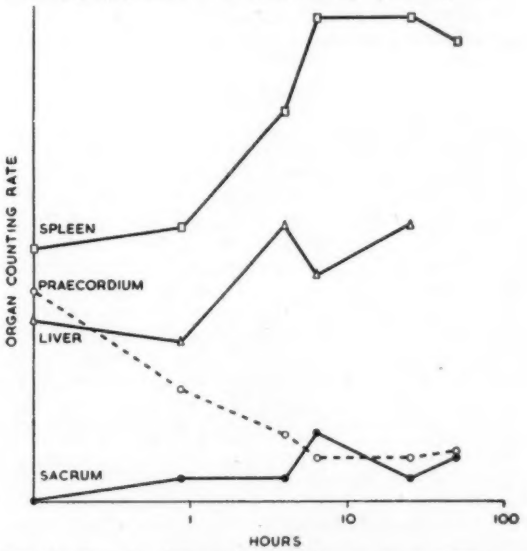

FIG. 6.—Case 2. ^{59}Fe surface-counting in June, 1957 (pre-splenectomy).

(b) May, 1958.—^{59}Fe utilization, 19%. Plasma iron, 289 μg./100 ml. The counting rate over the sacrum did not rise at all. The initial counting rates over spleen and liver were higher than normal, but neither changed significantly until the spleen counting rate started to rise after 48 hours, and continued rising until the study ended at 100 hours. ^{51}Cr red-cell loss, 5.5% a day.

(c) June, 1958 (Post-splenectomy).—Performed when the haemoglobin level had become steady. ^{59}Fe utilization, 73%. Plasma iron, 287 μg./100 ml. ^{51}Cr red-cell loss, 3.3% a day. Surface pattern unsatisfactory for technical reasons.

(d) September, 1958.—^{59}Fe utilization, 57%. Surface pattern (Fig. 7) shows a greater rise in counting rate over

the sacrum than in previous studies, but this was still subnormal. The initial counting rate over the liver was raised and showed a peak at about 24 hours.

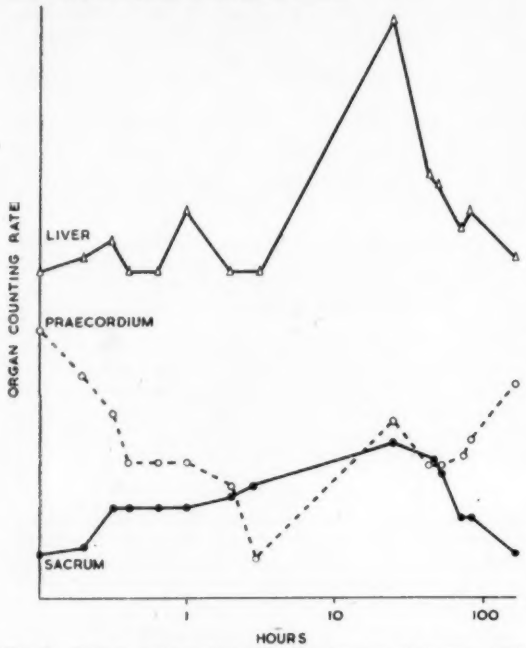

FIG. 7.—Case 2. ^{59}Fe surface-counting pattern in September, 1958 (post-splenectomy).

Discussion

In both patients there had been great difficulty in raising the haemoglobin level before splenectomy, even with frequent transfusions. The main haematological value of splenectomy lay in its effect on the haemoglobin, which was maintained at a reasonable level without therapy for 12 months in Case 1 (apart from one transfusion after a haematemesis) and for three and a half months in Case 2. Fourteen months after splenectomy the first patient again became anaemic. Although in the peripheral blood there was still evidence of the underlying myeloproliferative disorder in the shape of immature leucocytes and red cells, the anaemia was of iron-deficiency type with a low plasma iron and could be predominantly ascribed to the gastro-intestinal bleeding.

Conventional haematological investigations often fail to establish the relative importance of impaired erythropoiesis and increased red-cell destruction in the pathogenesis of anaemia in myelofibrosis. It is not therefore usually possible to decide if improvement after splenectomy is due solely to lengthening of the effective red-cell life. In the cases here reported there was evidence that after splenectomy not only was red-cell destruction decreased but red-cell production was strikingly increased.

The use of ^{59}Fe in the assessment of erythropoiesis is well established, although the sources of error in the interpretation of the results are not always considered (Wetherley-Mein and Hutt, 1960). An important source of difficulty is the effect of variations in the size of the plasma iron pool immediately labelled with the isotope. In the above cases there were only small changes in the size of the plasma iron pool when the ^{59}Fe utilizations were determined immediately before and four weeks after splenectomy. In each case the large increase in ^{59}Fe utilization may be taken to indicate increased erythropoiesis, unless some as yet unknown factor was operating to depress utilization before splenectomy.

The ^{59}Fe surface-counting patterns shown originally in both patients (Figs. 4 and 6) are commonly seen in myelofibrosis, and their interpretation has been discussed elsewhere (Hutt, Jones, and Wetherley-Mein, 1959). They are not adequately explained by variations in the size of the liver and spleen, the degree of anaemia, or the level of red-cell production. Variations in the size of the iron pool labelled affect the rate of removal of ^{59}Fe by various organs, but do not determine the differential distribution of the isotope. The flattened sacral marrow curve and splenic peak in myelofibrosis do not necessarily vary with the level of red-cell production. It is of interest that in both these cases the marrow curve tended to return towards normal after splenectomy (Figs. 5 and 7), although in neither case was a normal pattern fully established. This change further supports the view that the improved ability of these patients to maintain their haemoglobin levels resulted from increased erythropoiesis as well as from lengthened red-cell life.

Reticulocytes were plentiful in the peripheral blood of these patients at times when red-cell production was much reduced. This apparent discrepancy has been observed in myelofibrosis by others (Nathan and Berlin, 1959), and may be due to an alteration in the phase life of the reticulocyte in the circulation.

It is often held that in this disease the spleen is an important site of erythropoiesis and that splenectomy is therefore contraindicated. However, despite histological evidence of numerous red-cell precursors in the spleen, the results in the cases reported here suggest that in some cases not only may the splenic contribution to effective erythropoiesis be insignificant but that the spleen may itself inhibit red-cell production elsewhere. In one of their cases Nathan and Berlin (1959) obtained evidence that the spleen was producing red cells but failing to discharge them into the circulation. The presence of red-cell precursors in histological preparations of the spleen does not necessarily imply the efficient delivery to the circulation of normal red cells.

In reported cases of myelofibrosis where there has been benefit from splenectomy, the usual indications for operation have been uncontrollable haemolytic anaemia or persistent thrombocytopenia, but it seems that increasing difficulty in the management of an anaemia due to failure of red-cell production may be an additional indication for splenectomy. We have observed other cases of myelofibrosis subjected to splenectomy where the patient's ability to maintain his haemoglobin level after operation has been increased in some, unchanged in others, and occasionally diminished. A method of predicting the effects of splenectomy on red-cell production would be valuable. In one case of myelofibrosis in which ^{59}Fe and ^{51}Cr studies were made we observed no increase in red-cell production after splenectomy. In this patient's bone-marrow there was a total absence of red-cell precursors. In the marrow of the two cases reported above, scattered islands of red-cell precursors could be found. It may be that a failure to find in the marrow any evidence of active erythropoiesis, however slight, indicates that no increase in red-cell production can be expected after splenectomy.

Further work is necessary to define the indications for splenectomy, but we think it premature to conclude that it is never indicated in this condition.

Increasing hepatomegaly after splenectomy in myelofibrosis has been described, but has not necessarily been associated with either jaundice or rapid clinical deterioration—for example, Case J. G. of Nathan and Berlin (1959). We have observed this change after splenectomy in other myeloproliferative disorders in the absence of haematological deterioration. During the three months following operation in Case 2 reported here, the liver enlarged considerably and an obstructive-type jaundice was present for the last month of life. Necropsy was not allowed, and the pathology of this jaundice is unknown. It remains to be seen whether the possibility of subsequent liver damage should contraindicate splenectomy in this condition.

A brief consideration of the theoretical implications of our findings is appropriate. The relationship between the spleen and the bone-marrow remains obscure, and the relative roles of red-cell hypersequestration and marrow inhibition by the spleen are still debated (Doan, 1949; Dameshek, 1955). It is difficult to interpret the results obtained in these two patients wholly in terms of splenic hypersequestration of red cells. The increased red-cell production after splenectomy implies splenic inhibition of erythropoiesis. This finding lends support to the view that the spleen may not only be an important site of red-cell destruction, but may on occasion simultaneously limit effective red-cell production.

Summary

In two cases of myelofibrosis splenectomy was followed by considerable haematological improvement.

Evidence was obtained that erythropoiesis was increased after splenectomy in each case. The significance of this finding is discussed.

The indications for and against splenectomy in myelofibrosis are still uncertain, but it is premature to conclude that the operation is never indicated in this condition.

We are grateful to Professor A. C. Dornhorst and to Dr. J. L. Pinniger for helpful criticism. We thank the staff of St. Thomas's Hospital for permission to study these patients. The expenses of this investigation were partly borne by the hospital's endowment fund.

REFERENCES

Andreasen, A. P. (1958). *Myelofibrosis.* Munksgaard, Copenhagen.
Bothwell, T. H., and Mallett, B. (1955). *Biochem. J.*, **59**, 599.
Brit. med. J., 1960, **1**, 625.
Claman, M. A., and Collier, W. J. (1952). *Arch. intern. Med.*, **89**, 431.
Dameshek, W. (1955). *Bull. N.Y. Acad. Med.*, **31**, 113.
Doan, C. A. (1949). Ibid., **25**, 625.
Donhauser, J. L. (1908). *J. exp. Med.*, **10**, 559.
Edwards, H. C. (1951). *Lancet*, **2**, 601.
Franks, R. B., and Richardson, J. S. (1952). *Proc. roy. Soc. Med.*, **45**, 30.
Green, T. W., Conley, C. L., Ashburn, L. L., and Peters, H. R. (1953). *New Engl. J. Med.*, **248**, 211.
Hickling, R. A. (1937). *Quart. J. Med.*, **6**, 253.
Hutt, M. S. R., Jones, N. F., and Wetherley-Mein, G. (1959). *Trans. 7th Congr. Europ. Soc. Haemat., London.*
—— Pinniger, J. L., and Wetherley-Mein, G. (1953). *Blood*, **8**, 295.
Jackson, H., Parker, F., and Lemon, H. M. (1940). *New Engl. J. Med.*, **222**, 985.
Jones, N. F., Wetherley-Mein, G., Ingram, G. I. C., and Langmead, W. A. (1960). *J. clin. Path.*, **13**, 391.
Lancet, 1949, **2**, 756.
Learmonth, J. (1951). *Brit. med. J.*, **2**, 67.
Nathan, D. G., and Berlin, N. I. (1959). *Blood*, **14**, 668.
Panels in Therapy (1955). Ibid., **10**, 550.
Reich, C., and Rumsey, W., jun. (1942). *J. Amer. med. Ass.*, **118**, 1200.
Sanneman, E. H., McIlvanie, S. K., and Beard, M. F. (1950). *J. Kentucky med. Ass.*, **48**, 453.
Shinton, N. K. (1957). *Brit. med. J.*, **2**, 1395.
Videbaek, A. (1956). *Acta haemat. (Basel)*, **15**, 235.
Wetherley-Mein, G., and Hutt, M.S.R. (1960). In *Recent Advances in Clinical Pathology*, series 3, p. 241, edited by S. C. Dyke. Churchill, London.
—— —— Langmead, W. A., and Hill, M. J. (1956). *Brit. med. J.*, **1**, 1445.

EFFECT OF AN ANTIBACTERIAL NASAL CREAM ON NASAL COLONIZATION AND INFECTION IN THE NEWBORN

BY

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The increasing incidence of staphylococcal infections in maternity hospitals has become a matter of some concern. Although most of the infections which occur in babies in hospitals are superficial and mild, severe infections—for example, pneumonia and pemphigus—may arise, and some may also develop after the baby has left hospital—for example, osteomyelitis. Similarly, severe staphylococcal infections are not common in parturient women while in hospital but may develop later—for example, breast abscess.

If the number of staphylococci in the environment could be lowered an appreciable reduction in the number of lesions due to these organisms might be found. A high proportion of babies' noses become colonized with staphylococci during the first few days of life (Cunliffe, 1949; Parker and Kennedy, 1949; Cook *et al.*, 1958; Gillespie *et al.*, 1958). Not only may this colonization lead to infections in hospital but a large proportion of babies may leave hospital carrying pathogenic staphylococci, which may give rise to serious sepsis in the baby or in the mother during the weeks after discharge. These staphylococci are often retained for many months (Ludlam, 1953; Hurst, 1957).

It has been shown that the use of an antibiotic nasal cream by the hospital staff reduces the incidence of staphylococcal cross-infection in a ward (Gould and Allan, 1954; Rountree *et al.*, 1956), but the routine use of a nasal cream by hospital staff presents considerable administrative difficulties. It was decided, therefore, to carry out a trial of the application of an antibacterial nasal cream (" naseptin ") to the anterior nares of babies from birth and to study the effect on nasal colonization and on the incidence of infection.

Methods

The wards in which the investigation was carried out are large and old-fashioned, holding 14 to 16 beds; there are very few side-rooms, and the facility for isolation of mother and child is limited. The nurseries hold up to 15 cots, and the babies remain therein, apart from feeding-times and a period of five hours each day which they spend with their mothers. Masks are not worn by the paediatric nursing and medical staff nor by the mothers. The cord is tied with sterile ligatures, and

sterile collodion is applied to the cut stump, which is treated twice daily with 1% chlorhexidine in 90% spirit. The babies are bathed on the fourth day, and thereafter on alternate days until discharge from hospital, care being taken to keep the cord dry.

Groups of babies had cream containing 0.1% chlorhexidine hydrochloride and 0.5% neomycin sulphate (naseptin) applied to the anterior nares once daily by means of a glass rod of 5 mm. diameter. Swabs were taken within 24 hours of birth and on the fourth and eighth days, in order to show the effect on the rate of colonization. Swabs were taken 24 hours after the last application of cream. Swabs were also taken from a comparable group of babies without the application of cream. In a further group the mothers also used the antibacterial cream.

All the swabs were plated on to agar plates containing 0.01% phenolphthalein diphosphate and phosphatase-positive colonies subcultured for further investigation. (The term staphylococci in this paper refers to coagulase-positive *Staph. aureus*.) Broth or agar containing 10% NaCl was not used. The incorporation of 0.1% lubrol in the agar was not found to increase the number of staphylococci isolated, and was discontinued after a trial period.

Swabs were also taken from all lesions which developed in the babies while in hospital, and the infections referred to later are only those from which staphylococci were isolated.

The incidence of infections in mothers and babies after leaving hospital was determined either by health visitors or by a postal questionary at two months.

Most of the staphylococci isolated from carriers were sent for phage-typing in order to determine more accurately the relationship between the staphylococci isolated from various sites and individuals.

Results

Initially there were 132 babies in the control group and 113 in the group in which nasal cream was used.

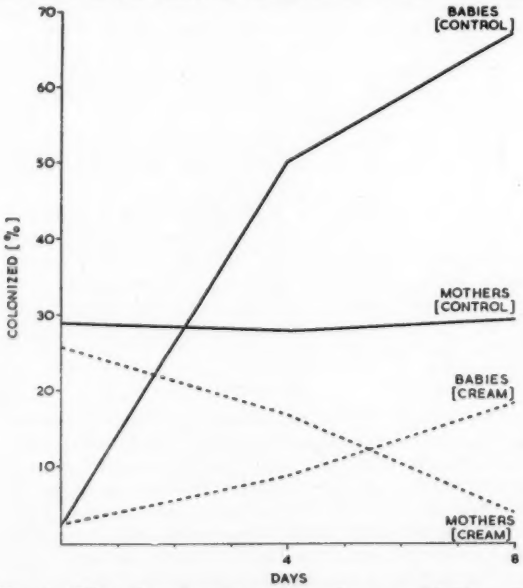

FIG. 1.—Effect of nasal cream on the carriage rate of babies and mothers.

TABLE I.—*Infections in Babies in Hospital and During First Two Months after Leaving Hospital Related to Application of Nasal Cream*

	No. of Babies	Infections in Hospital		No. of Babies	Infections After Discharge		Total %
		No.	%		No.	%	
No cream ..	113	13	11·6	98	23	23·5	35·1
Cream ..	108	8	7·4	105	13	12·4	19·8

Staphylococci were found in 2.5% of babies in the first 24 hours after birth, but thereafter colonization was rapid in the control group, so that one half showed staphylococci on the fourth day and 88 babies (67%) were positive on the eighth day. When the nasal cream was used only 21 (18%) of the babies' noses had been colonized by the eighth day (Fig. 1).

During their stay in hospital the proportion of mothers who carried staphylococci did not rise, being 29% on admission, 27.5% on the fourth day, and 29% on discharge; but the use of the nasal cream by the mothers steadily reduced the carrier rate to 16.5% on the fourth day and 3.2% on discharge (Fig. 1). In a group of babies whose mothers also used the nasal cream there was no further effect on the colonization of the babies' noses.

In the control group 13 (11.6%) out of 113 babies developed staphylococcal lesions while in hospital, as compared with 8 (7.4%) out of 108 in the treated babies. Of the 98 babies in the control group who were followed up after discharge from hospital, 23 (23.5%) reported an infection, whereas in the treated group only 13 (12.4%) out of 105 developed lesions (Table I). As

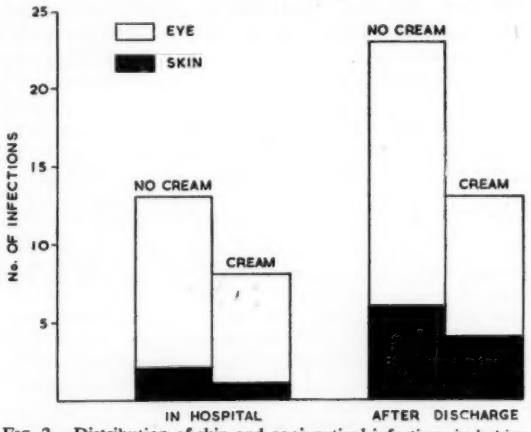

FIG. 2.—Distribution of skin and conjunctival infections in babies while in hospital and during the first two months at home.

is shown in Fig. 2, the greater difference was in the number of conjunctival infections; these are high compared with other reports, as we have included all babies with discharge from the inner canthus but without actual conjunctivitis. Most of these infections cleared in 24 hours. If the incidence of infection is related to actual carriage of staphylococci in the nose this difference is emphasized (Table II).

Of the 389 staphylococci that were phage-typed, 231 belonged to group I and 87 to group III. The two most common types in group I were 52A and 29/52 or 29/52/80; together these two comprised 60% of the group I staphylococci. In group III, types 7/47/53/54+ and 77 together made up 56% of the group.

During the period of the trial these four types comprised 52% of the staphylococci obtained on the eighth day from various sites in babies, but only 27% in the case of the mothers. These four types formed 43% of the staphylococci isolated from members of the staff.

TABLE II.—*Infections in Babies in Hospital and During First Two Months after Leaving Hospital Related to Nasal Carriage of Staphylococci*

	No. of Babies	Infections in Hospital		No. of Babies	Infections After Discharge		Total %
		No.	%		No.	%	
Carriers ..	107	14	13·1	92	22	23·9	37·0
Non-carriers ..	109	6	5·5	102	12	11·7	17·2

Discussion

The association between nasal carriage of staphylococci and septic lesions has been known for some years —for example, industrial wounds (Williams and Miles, 1949), recurrent furunculosis (Valentine and Hall-Smith, 1952), and recurrent styes (Roodyn, 1954). Little has been done to control staphylococcal cross-infection routinely by preventing and clearing nasal colonization, although there have been a number of reports of the effect of nasal clearance as an emergency method during epidemics—the local application of an antibiotic nasal cream being the most common method employed. Gould and Allan (1954) and Rountree *et al.* (1956) have shown that a considerable reduction in staphylococcal cross-infection can be obtained by the nasal treatment of hospital staff. Gould and Cruickshank (1957) showed that by reducing nasal carriage in individuals recurrent lesions due to staphylococci were greatly reduced. Gillespie and Adler (1957) reported that the use of a nasal cream by staff and patients in a children's hospital was effective in controlling an epidemic of infections due to *Staph. pyogenes* type 80. Klein and Rogers (1959) and Wilkinson (1959), using a nasal cream, and Baker and Christie (1959), using nasal antibiotic drops, have reported similar success in maternity hospitals.

Since we began our investigation Weinstein (1959) has shown that nasal colonization often precedes the infection of wounds, and Williams *et al.* (1959) have demonstrated that the incidence of wound sepsis in a surgical ward was only 2% in non-carriers, whereas it was 7.1% in carriers. In about half of these infections the same staphylococcus was found in the nose and the wound. But Williams *et al.* also showed that 35% of the carriers of the more virulent staphylococci, as determined by phage-typing, developed wound sepsis, and all these wound infections were due to staphylococci of the same type as those in the nose; similar results were obtained in patients who developed sepsis at other sites. They suggest that the incidence of infection might be reduced if nasal colonization could be prevented, although Weinstein had little success with this method.

The problem with the newborn is slightly different, as they are almost always born free of staphylococci, and the aim must be to prevent their becoming colonized with hospital staphylococci, some of which are potentially more dangerous and often more resistant to antibiotics. Although a number of babies who are discharged from hospital free from staphylococci will acquire them later, there is a much greater chance that these staphylococci will be of a less virulent and less resistant type and therefore less likely to cause severe sepsis.

In the trial reported here, 67% of the untreated babies became nasal carriers by the eighth day. This proportion is a little lower than that reported by Cunliffe (1949), Parker and Kennedy (1949), Cook *et al.* (1958), and Gillespie *et al.* (1958), but the use of the antibacterial nasal cream was effective in reducing the carriage rate to less than one-third—namely, 18%. There was also a considerable reduction in the number of conjunctival infections due to staphylococci in the treated group. The decrease in infections was also apparent during the two months after discharge from hospital (Fig. 2). Although most eye infections are themselves of little consequence they represent a form of colonization and allow transfer of hospital staphylococci to the home. When the incidence of infections is related to actual nasal carriage (Table II), the difference in infection rates is more obvious, being more than twice as high in carriers than in non-carriers. This ratio is very similar to that found in the newborn by Manfield *et al.* (1960) and in surgical patients by Williams *et al.* (1959).

Further evidence to show the importance of nasal carriage can be obtained from the phage-types in this series. Four types—52A, 29/52 or 29/52/80, 7/47/53/54+, and 77—formed 52% of the staphylococci isolated from carrier sites on the babies. During 1959, 133 staphylococci from various lesions were typed, and 54% were found to belong to these four types.

Although the carrier rate amongst the mothers remained stationary at 29%, the type of staphylococci changed, as was noted by Barber *et al.* (1953). Within 24 hours of delivery 18% of the maternal staphylococci belonged to the most common types present in the hospital during the relevant period, but by the eighth day the figure had risen to 27%. This change is not so marked as that found by Barber *et al.*—an increase of from 6% to 35% in type 52A—but their patients were swabbed on admission, whereas ours were swabbed after delivery and had been in contact with hospital staff for a variable period of time.

For many years it has been thought that the staphylococcus causing breast abscesses most often comes from the baby's and not the mother's nose (Colbeck, 1949; Cook *et al.*, 1958; Knight and Nolan, 1959), although the evidence for this statement is not always unequivocal. However, Wilkinson (1959) has shown that in 40 cases of breast abscess a staphylococcus of the same phage-type was present in 27 of the corresponding babies' noses. Unfortunately, the six patients with a breast abscess in our series were seen at other hospitals and no pus was obtained; but an abscess occurred in five mothers of babies in the control group, and four of these babies were carriers of staphylococci on discharge.

There have been a number of reports on methods for the prevention of colonization of babies' noses. Baldwin *et al.* (1957) found that hexachlorophane baths provided the best method of reducing nasal colonization. Cook *et al.* (1958) compared results with chlorhexidine hand-cream, sterilized bedding, individual gowns, and triple dye painted on the umbilicus. The last method was the most effective, but reduced nasal carriage only from 100% to 69%. Gillespie *et al.* (1958), while using hexachlorophane dusting powder, noted that nasal colonization was reduced by one-half to 40%. Manfield *et al.* (1960) compared triple dye alone, triple dye combined with ultra-violet irradiation of the nursery, and triple dye combined with daily hexachlorophane baths. The first two methods reduced colonization to 65% and the third to 55%.

It is apparent that the application of an antibacterial cream to the anterior nares is the best method of reducing colonization in newborn infants. Gould (1955), using an antibiotic cream, reduced the carriage rate in adults to 25%, but the use of an antibiotic likely to produce resistant strains is a disadvantage. Baker and Christie (1959) used neomycin drops in infants with good clearance, and this antibiotic has the advantage of not adversely affecting the general sensitivity patterns although resistance to neomycin itself has been described (Quie *et al.*, 1960). We have used a combination of neomycin and chlorhexidine, with a reduction in nasal carriage rate to 18% in babies and 3.5% in mothers and a marked reduction in the infection rate. No harmful effects were noted during the trial, and *in vitro* observations have not shown any resistance to neomycin when it is combined in this manner with chlorhexidine (K. G. Green, personal communication, 1960).

The recent work of Gillespie *et al.* (1958), Simpson *et al.* (1960), and Corner *et al.* (1960), using hexachlorophane dusting powder, suggests that a combination of both methods might be of further benefit, and such a trial is now in progress.

Summary

A trial of combined neomycin/chlorhexidine nasal cream ("naseptin") was carried out in an attempt to reduce nasal colonization by staphylococci in newborn infants and mothers in a maternity hospital.

There was a definite reduction of nasal colonization in both groups.

The incidence of infections both in hospital and in the two-months period after discharge was appreciably reduced, more particularly in the group who were not nasal carriers of staphylococci.

The majority of the staphylococci that were phage-typed belonged to group I.

It is suggested that daily use of nasal cream combined with regular powdering with an antiseptic dusting powder might produce a further fall in colonization and infection in the newborn period.

We thank Dr. M. T. Parker for carrying out the phage-typing; Dr. K. G. Green, of Imperial Chemical Industries Ltd. (Pharmaceuticals Division) for arranging a generous supply of naseptin and for his co-operation throughout the trial; Mr. P. Stenton, F.I.M.L.T., who carried out a great deal of the technical work; and especially our paediatric and obstetric colleagues, without whose friendly co-operation the trial would not have been possible.

REFERENCES

Baker, W. H. J., and Christie, D. R. (1959). *Brit. med. J.*, **2**, 192.
Baldwin, J. N., Rheins, M. S., Sylvester, R. F., and Shaffer, T. E. (1957). *Amer. J. Dis. Child.*, **94**, 107.
Barber, M., Wilson, B. D. R., Rippon, J. E., and Williams, R. E. O. (1953). *J. Obstet. Gynaec. Brit. Emp.*, **60**, 476.
Colbeck, J. C. (1949). *Canad. med. Ass. J.*, **61**, 557.
Cook, J., Parrish, J. A., and Shooter, R. A. (1958). *Brit. med. J.*, **1**, 74.
Corner, B. D., Crowther, S. T., and Eades, S. M. (1960). Ibid., **1**, 1927.
Cunliffe, A. C. (1949). *Lancet*, **2**, 411.
Gillespie, W. A., and Adler, V. G. (1957). Ibid., **1**, 632.
—— Simpson, K., and Tozer, R. C. (1958). Ibid., **2**, 1075.
Gould, J. C. (1955). *J. Hyg. (Camb.)*, **53**, 379.
—— and Allan, W. S. A. (1954). *Lancet*, **2**, 988.
—— and Cruickshank, J. D. (1957). Ibid., **2**, 1157.
Hurst, V. (1957). *J. Hyg. (Camb.)*, **55**, 299.
Klein, J. O., and Rogers, E. F. H. (1959). *New Engl. J. Med.*, **260**, 1012.
Knight, I. C. S., and Nolan, B. (1959). *Brit. med. J.*, **1**, 1224.
Ludlam, G. B. (1953). *J. Hyg. (Camb.)*, **51**, 64.
Manfield, P. A., Shooter, R. A., and Lidwell, O. M. (1960). *Brit. med. J.*, **1**, 1098.
Parker, M. T., and Kennedy, J. (1949). *J. Hyg. (Camb.)*, **47**, 213.
Quie, P. G., Collin, M., and Cardle, J. B. (1960). *Lancet*, **2**, 124.
Roodyn, L. (1954). *Brit. med. J.*, **2**, 1322.
Rountree, P. M., Heseltine, M., Rheuben, J., and Shearman, R. P. (1956). *Med. J. Aust.*, **1**, 528.
Simpson, K., Tozer, R. C., and Gillespie, W. A. (1960). *Brit. med. J.*, **1**, 315.
Valentine, F. C. O., and Hall-Smith, S. P. (1952). *Lancet*, **2**, 351.
Weinstein, H. J. (1959). *New Engl. J. Med.*, **260**, 1303.
Wilkinson, B. M. (1959). *J. Obstet. Gynaec. Brit. Emp.*, **66**, 394.
Williams, R. E. O., Jevons, M. P., Shooter, R. A., Hunter, C. J. W., Girling, J. A., Griffiths, J. D., and Taylor, G. W. (1959). *Brit. med. J.*, **2**, 658.
—— and Miles, A. A. (1949). *Spec. Rep. Ser. med. Res. Coun. (Lond.)*, No. 266.

SECRETION OF ABH ANTIGENS IN PEPTIC ULCERATION AND GASTRIC CARCINOMA*

BY

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Various hypotheses have been proposed to explain the association of the ABO blood groups with disease processes. Best-established are the association with peptic ulceration characterized by an increased group O frequency and that for gastric carcinoma characterized by an increased group A frequency (Buckwalter *et al.*, 1958). Perhaps the most plausible explanation for the associations with peptic ulceration and gastric carcinoma is that the mucopolysaccharide ABH blood-group substances which are secreted into the gastro-intestinal tract protect the mucous membrane against ulcerogenic and carcinogenic agents (Aird *et al.*, 1954). This is a report of a study of secretion of mucopolysaccharide blood-group substance in peptic ulcer and gastric carcinoma patients.

Materials and Methods

Since 1956 peptic ulcer and gastric carcinoma patients admitted to the University of Iowa and Iowa City Veterans Administration hospitals have provided clinical material for this study. The diagnoses have been established on morphological grounds in all patients with gastric carcinoma and in two-thirds of those with peptic ulcer; and in the remainder on the basis of a typical history with positive upper gastro-intestinal *x*-ray studies. Blood and saliva samples and relevant history have been obtained for each patient. A qualitative determination of the ABH substance in saliva has been done, employing the isohaemagglutination test, using anti-H substance prepared from seeds of *Ulex europaeus*, and A and B antisera. Controls have been provided by a random sample of hospital personnel and patients with diagnoses other than those being studied. The differences between the secretor and non-secretor percentages of the patients and the controls have been examined for statistical significance by the chi-square (χ^2) method.

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Results

The raw data are recorded in Table I. Controls, and duodenal ulcer, gastric ulcer, and gastric carcinoma patients are subdivided by blood group, secretor status, and sex. Blood groups A and AB are further divided into A_1, A_2, A_1B, A_2B. The results of the statistical analysis of these data are recorded in Table II. The results of only those comparisons are given which are of importance in evaluating the findings. Blood groups B and AB are combined in the analyses. The smallness of the numbers of patients in these categories makes their analysis as separate groups meaningless. Observe that the controls and various patient categories are examined for heterogeneity. Some heterogeneity is present in the female controls, but is not significant.

Secretor status of the patients is compared with that of controls. A significant increase in non-secretion is found in duodenal ulcer patients when they are compared with controls ($P<0.001$). When the secretor status of duodenal ulcer patients of the different blood groups is examined, note that those with blood group A (A_1, A_2) compared with controls of blood group A show a statistically significant increase in non-secretion ($\chi^2=10.364$; $P<0.01$). Of less statistical significance were the differences between duodenal ulcer patients of group O and the O controls ($\chi^2=6.272$; $P<0.02$), A_1, A_1B patients and controls ($\chi^2=6.438$; $P<0.02$), and A_2, A_2B patients and controls ($\chi^2=3.565$; $P<0.10$). Observe that the secretor status of gastric ulcer and gastric carcinoma patients did not differ significantly from that of the controls.

TABLE I.—*Secretor and Blood-group Status of Patients and Controls*

	Total Patients	Blood Group %	Secretors M	Secretors F	Secretors Total	Secretors %	Non-secretors M	Non-secretors F	Non-secretors Total	Non-secretors %
Controls										
O	563	44·65	230	197	447	79·40	69	47	116	20·60
A	512	40·60	233	154	387	75·59	75	50	125	24·41
A_1	424	33·62	195	127	322	75·94	54	48	102	24·06
A_2	88	6·98	38	27	65	73·86	21	2	23	26·14
B	144	11·42	66	41	107	74·31	19	18	37	25·69
AB	42	3·33	20	10	30	71·43	7	5	12	28·57
A_1B	31	2·46	13	9	22	70·97	6	3	9	29·03
A_2B	11	0·87	7	1	8	72·73	1	2	3	27·27
Total	1,261	100·00	569	402	971	77·00	170	120	290	23·00
Duodenal Ulcer										
O	257	53·65	156	28	184	71·60	62	11	73	28·40
A	163	34·03	83	19	102	62·58	44	17	61	37·42
A_1	140	29·23	75	15	90	64·29	37	13	50	35·71
A_2	23	4·80	8	4	12	52·17	7	4	11	47·83
B	44	9·18	22	7	29	65·91	13	2	15	34·09
AB	15	3·13	8	3	11	73·33	3	1	4	26·67
A_1B	10	2·09	4	3	7	70·00	2	1	3	30·00
A_2B	5	1·04	4	0	4	80·00	1	0	1	20·00
Total	479	99·99	269	57	326	68·06	122	31	153	31·94
Gastric Ulcer										
O	104	56·52	57	18	75	72·12	23	6	29	27·88
A	54	29·35	35	6	41	75·93	10	3	13	24·07
A_1	43	23·37	28	5	33	76·74	7	3	10	23·24
A_2	11	5·98	7	1	8	72·73	3	0	3	27·27
B	19	10·33	13	3	16	84·21	2	1	3	15·79
AB	7	3·80	4	1	5	71·43	2	0	2	28·57
A_1B	3	1·63	2	0	2	66·67	1	0	1	33·33
A_2B	4	2·17	2	1	3	75·00	1	0	1	25·00
Total	184	100·00	109	28	137	74·46	37	10	47	25·54
Gastric Carcinoma										
O	43	36·44	26	8	34	79·07	9	0	9	20·93
A	61	51·69	29	18	47	77·05	7	7	14	22·95
A_1	54	45·76	25	17	42	77·78	5	7	12	22·22
A_2	7	5·93	4	1	5	71·43	2	0	2	28·57
B	10	8·47	5	3	8	80·00	2	0	2	20·00
AB	4	3·39	2	1	3	75·00	1	0	1	25·00
A_1B	4	3·39	2	1	3	75·00	1	0	1	25·00
A_2B	0	0·00	0	0	0	00·00	0	0	0	00·00
Total	118	99·99	62	30	92	77·97	19	7	26	22·03

In Table III the secretor status of patients with duodenal ulcer and gastric ulcer is examined as related to severity of the disease process. The five clinical groups into which the patients are divided are described in the first column. No evidence of heterogeneity was found in these data ($0.10<P$) for both duodenal and gastric ulcer.

TABLE II.—*Statistical Analysis of the Data*

Groups	χ^2	
Controls:		
Males O×A×(B+AB)	0·578	$0·10<P$
Females O×A×(B+AB)	4·875	$0·05<P<0·10$
Males×females	0·0	$0·10<P$
$A_1A_1B\times A_2A_2B$	0·267	$0·10<P$
Duodenal ulcer:		
Males O×A×(B+AB)	1·764	$0·10<P$
Females O×A×(B+AB)	3·290	$0·10<P$
Males×females	0·577	$0·10<P$
$A_1A_1B\times A_2A_2B$	0·737	$0·10<P$
Patients×controls	14·585	$P<0·001$
,, O× ,, O	6·272	$0·01<P<0·02$
,, A× ,, A	10·364	$0·001<P<0·01$
,, B+AB×controls B+AB	1·012	$0·10<P$
,, $A_1A_1B\times$,, A_1A_1B	6·438	$0·01<P<0·02$
,, $A_2A_2B\times$,, A_2A_2B	3·565	$0·05<P<0·10$
,, A,B,AB× ,, A,B,AB	10·746	$0·001<P<0·01$
Gastric ulcer:		
Males O×A×(B+AB)	1·317	$0·10<P$
Females O×A×(B×AB)	0·0	$0·10<P$
Males×females	0·0	$0·10<P$
$A_1A_1B\times A_2A_2B$	0·0	$0·10<P$
Patients×controls	0·557	$0·10<P$
,, O× ,, O	2·386	$0·10<P$
,, A× ,, A	0·0	$0·10<P$
,, B+AB×controls B+AB	0·896	$0·10<P$
,, $A_1A_1B\times$,, A_1A_1B	0·0	$0·10<P$
,, $A_2A_2B\times$,, A_2A_2B	0·0	$0·10<P$
Gastric carcinoma:		
Males O×A×(B+AB)	1·380	$0·10<P$
Females O×A×(B+AB)	3·476	$0·10<P$
Males×females	0·231	$0·10<P$
$A_1A_1B\times A_2A_2B$	1·355	$0·10<P$
Patients×controls	0·061	$0·10<P$
,, O×controls O	0·0	$0·10<P$
,, A× ,, A	0·099	$0·10<P$
,, B+AB×controls B+AB	0·378	$0·10<P$
,, $A_1A_1B\times$,, A_1A_1B	0·106	$0·10<P$
,, $A_2A_2B\times$,, A_2A_2B	0·0	$0·10<P$

TABLE III.—*Secretor Status Related to Severity of Disease*

	Duodenal Ulcer S.	Duodenal Ulcer %	Duodenal Ulcer N.S.	Duodenal Ulcer %	Gastric Ulcer S.	Gastric Ulcer %	Gastric Ulcer N.S.	Gastric Ulcer %
Medical therapy; good response	84	64·62	46	35·38	33	78·57	9	21·43
Medical therapy; poor response	81	72·32	31	27·68	11	55·00	9	45·00
Surgical therapy; good response	101	66·45	51	33·55	37	74·00	13	26·00
Surgical therapy; poor response	47	71·21	19	28·79	13	59·09	9	40·91
Surgical therapy; poor response after more than one operation	6	60·00	4	40·00	0	0·00	0	0·00
Total	319	67·87	151	32·13	94	70·15	40	29·85

S.=Secretor. N.S.=Non-secretor.

Discussion

When the differences between the ABO blood-group percentages of the 479 duodenal ulcer, 184 gastric ulcer, and 118 gastric carcinoma patients included in this study are compared with the blood-group percentages of the 1,261 controls for this study, the differences for gastric ulcer and gastric carcinoma patients from the controls are found to be greater than those for duodenal ulcer patients. However, when the statistical significance of these differences is examined we obtain the following: duodenal ulcer ($\chi^2=13.624$; $P<0.01$), gastric ulcer ($\chi^2=10.432$; $P<0.02$), gastric carcinoma ($\chi^2=5.680$; $0.10<P$). The blood-group percentage differences in the gastric ulcer and gastric carcinoma patients are also greater than those previously

found in much larger groups of patients (Buckwalter *et al.*, 1958). These discrepancies between the size of the blood-group percentage differences and the levels of statistical significance emphasize the need for large numbers of patients in these investigations if statistically valid conclusions are to be obtained, and illustrate how overemphasis of differences in the blood-group frequencies might lead to erroneous conclusions.

The suggestion of heterogeneity in the female controls, female duodenal ulcer patients, and female gastric carcinoma patients is not statistically significant. It seems probable, supported by the findings of Clarke *et al.* (1956), that these apparent differences are related to the volume of the data and may disappear if sufficient data are obtained.

This study confirms the increased percentage of non-secretors among patients with duodenal ulcer and the absence of any increase of non-secretion in gastric ulcer patients as reported by Clarke *et al.* (1959). However, as indicated before, and contrary to Clarke *et al.* (1955), a statistically significant increase in the frequency of blood group O in gastric ulcer patients was found similar to that found in the previous study. Also, an excess of group O was found in the propositi of both gastric ulcer and duodenal ulcer patients when the propositi were compared with their siblings (Van Scoy and Buckwalter, in preparation). Therefore, results of sibship and blood-group frequency studies are similar for gastric and duodenal ulcer, while the results of secretor studies differ for these two disease processes. This contradiction may be real or specious, and awaits the accumulation of more data for proper interpretation.

The secretion findings in the duodenal ulcer patients are consistent with the hypothesis that the mucopolysaccharide blood-group substances, by coating the gastro-intestinal mucosa, protect it against ulceration, and therefore could explain the association of blood group and duodenal ulcer. Our results suggest that most important is whether or not any ABH blood-group substances are secreted. Clarke *et al.* (1959), using fucose as an index of the mucopolysaccharide blood-group substance content in saliva, found evidence that the total content of the blood-group substances (ABH and Le^a) did not differ significantly between duodenal ulcer patients and their controls. This suggests that the secretor effect is related to ABH mucopolysaccharides rather than being a non-specific polysaccharide effect. Evidence against the hypothesis of ABH secretion as an explanation for the blood-group findings in patients with gastric ulcer and gastric carcinoma is provided by the close agreement of the secretor/non-secretor percentages of these patients with the controls.

Aird (1955) suggested that blood-group substances might vary in their ability to confer protection on the gastro-intestinal mucosa, with H substance offering less protection and A and B substances more protection. This would account for the increased frequency of blood group O in duodenal ulcer patients, since persons of group O secrete only H substance. It would also lead one to expect a lower frequency of ulcer in secretors of groups A, B, and AB, and, conversely, a higher percentage of non-secretors in ulcer patients of blood groups A, B, and AB.

Our findings of a higher percentage of non-secretion in duodenal ulcer patients of group A than in those of group O support the concept of a group specific association. Clarke *et al.* (1955) found the highest non-secretor percentages in duodenal ulcer patients of blood group O, while Wallace *et al.* (1958) found the highest non-secretion percentage in patients of groups A, B, and AB. However, the data indicate that the association of duodenal ulceration to the overall non-type-specific ABH secretion is statistically much stronger, and therefore probably more important.

It is probable that duodenal ulcer is not a single disease entity. If this is true, increasing numbers of factors will be discovered which play parts in the aetiology and pathogenesis of duodenal ulcers. The secretion of mucopolysaccharide blood-group substances through a mechanical, immunological, or some other mechanism may be one of the factors. It is possible that these investigations will also help resolve the questions concerning the relationship between duodenal and gastric ulcer.

No indication was found of a correlation between the severity of the disease process and secretor status. It is possible that secreted mucopolysaccharide blood-group substances form only an initial protective barrier against ulceration. Once this barrier has been bridged, the secretor may not differ from the non-secretor.

The only finding of statistical significance when groups A and AB were subdivided into groups A_1, A_2, and A_1B, A_2B was when duodenal ulcer patients were compared with the controls. The statistically increased rate of non-secretion in A_1, A_1B patients simply reflects the increased non-secretion percentage in all group A patients.

Conclusions

A statistically significant increase in non-secretors of mucopolysaccharide blood-group substances was found in patients with duodenal ulcer compared with controls.

In addition to the increase in non-secretion in patients of all ABO blood groups, a secondary association characterized by the highest non-secretion rate in group A patients was noted.

No association of secretor status to severity of duodenal ulcer was found.

The percentages of non-secretors in gastric ulcer and gastric carcinoma patients do not differ significantly from the controls.

References

Aird, I. (1955). *Proc. roy. Soc. Med.*, **48**, 139.
—— Bentall, H. H., Mehigan, J. A., and Roberts, J. A. F. (1954). *Brit. med. J.*, **2**, 315.
Buckwalter, J. A., Tidrick, R. T., Knowler, L. A., Wohlwend, E. B., Colter, D. C., Turner, J. H., Raterman, L., Gamber, H. H., Roller, G. J., Pollock, C. B., and Naifeh, V. K. (1958). *J. Iowa St. med. Soc.*, **48**, 76.
Clarke, C. A., Cowan, W. K., Edwards, J. W., Howel-Evans, A. W., McConnell, R. B., Woodrow, J. C., and Sheppard, P. M. (1955). *Brit. med. J.*, **2**, 643.
—— Edwards, J. W., Haddock, D. R. W., Howel-Evans, A. W., McConnell, R. B., and Sheppard, P. M. (1956). Ibid., **2**, 725.
—— Price-Evans, D. A., McConnell, R. B., and Sheppard, P. M. (1959). Ibid., **1**, 603.
Wallace, J., Brown, D. A. P., Cook, I. A., and Melrose, A. G. (1958). *Scot. med. J.*, **3**, 105.

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THE ABO BLOOD GROUPS AND PEPTIC ULCERATION

A SURVEY OF 1,080 CASES ON SOUTH TEES-SIDE

BY

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The possibility of the relationship of the ABO blood groups to disease has been investigated by many workers during the past 40 years, and their results have been carefully analysed by Fraser Roberts (1957), who concluded that, in the case of duodenal ulceration, there was overwhelming evidence that persons with group O blood were 40% more susceptible than those of other groups. With regard to gastric ulcers, he was of the opinion that the figures are about intermediate between those of duodenal ulcers and the controls, even allowing for the fact that some of the ulcers near the pylorus may have been misclassified.

My own series consists of 1,080 peptic ulcer patients on whom I have performed partial gastrectomies since coming to Tees-side. Thus all cases are ulcers proved at laparotomy.

The controls were obtained from Fraser Roberts's (1953) analysis of the ABO blood-group records of the North of England Blood Transfusion Service. In this district are areas 67 to 72, inclusive, from which nearly all my patients have come. As the total number of donors in each section is given and not the number of donors in each blood group, the latter have been calculated from the percentage group-frequencies and then the total number of the donors in the whole area, the numbers of donors in each group, and, finally, the percentage group-frequencies in the whole area. It was considered that this would provide more accurate control figures for the purpose of this investigation. These are given in Table I.

TABLE I.—*Control Figures Obtained from 4,540 Blood Donors in South Tees-side. Compiled from Fraser Roberts* (1953)

	AB	A	B	O
Group numbers ..	132	1,873	386	2,149
,, frequencies	2·91%	41·26%	8·50%	47·33%
Highest	3·62%	42·31%	12·36%	50·39%
Lowest	2·18%	38·24%	7·75%	45·82%

Results

In Table II I have given an analysis of the blood groups in 722 cases of duodenal ulcer. This shows that there is an increase in the frequency of group O by 24.7% to 59.0%, compared with the control of 47.33%. Group A, on the other hand, shows a decrease of 15.8%. The decrease in group B is statistically significant, but the numbers in group AB are too small for sound conclusions.

Table III shows the results of 232 cases of gastric ulcer. These are further analysed in Tables IV and V, the former giving the results of 58 prepyloric ulcers and the latter the results of 171 lesser-curvature ulcers. In the prepyloric group there is an increase of those with group O blood of 18.7% compared with the controls. This is smaller than the corresponding rise in cases of duodenal ulcer, and instead of the fall in group A there is a slight increase. This increase in group O and the differences in the proportion of group O between duodenal (Table II) and prepyloric ulcers (Table IV) are not statistically significant.

With regard to the lesser-curvature ulcers, there appears to be no change in the percentage of group O compared with the controls, and the slight increase in group A cases is not significant. It is to be noted, however, that not one of the lesser-curve cases came from group B when one would expect 21 patients or 12.36% of the 171 cases. This is most significant, as is the excess of group AB patients ($p<0.01$).

Where the presence of duodenal and gastric ulceration is found in the same patient—and these comprise no fewer than 126 cases in the present series (Table VI)—

TABLE II.—*Blood Groups of 722 Cases of Duodenal Ulcer*

	AB		A		B		O	
Rhesus	+	−	+	−	+	−	+	−
Men	3	3	185	26	23	3	325	29
Women ..	4	3	37	3	6	—	68	4
Total ..	7	6	222	29	29	3	393	33
Total excluding Rh factor ..	13		251		32		426	
Group frequency	1·80%		34·76%		4·43%		59·00%	
Variation from control ..	−38·1%		−15·8%		−52·1%		+24·7%	

TABLE III.—*Blood Groups of 232 Cases of Gastric Ulcer*

	Prepyloric				Lesser Curve				Greater Curve			
	AB	A	B	O	AB	A	B	O	AB	A	B	O
Men ..	—	19	—	16	10	64	—	52	—	—	—	—
Women ..	3	4	—	16	3	13	—	29	—	3	—	—
Total ..	3	23	—	32	13	77	—	81	—	3	—	—
% of all G.U. ..	1·3	9·9	—	13·8	5·6	33·2	—	34·9	—	1·3	—	—

TABLE IV.—*Variations from Control of 58 Cases of Prepyloric Ulcer*

	AB	A	B	O
Numbers ..	3	23	—	32
% of prepyloric ..	5·2	39·7	—	55·2
Variation from control	+78·7%	+3·8%	—	+18·7%

TABLE V.—*Variations from Control of 171 Cases of Lesser-curvature Gastric Ulcers*

	AB	A	B	O
Numbers ..	13	77	—	81
% of lesser curvature	7·6	45·0	—	47·4
Variation from control	+161·2%	+9·1%	—	+0·1%

TABLE VI.—*Blood Groups of 126 Cases of Combined Duodenal and Gastric Ulcer*

	Prepyloric				Lesser Curve				Greater Curve			
	AB	A	B	O	AB	A	B	O	AB	A	B	O
Men ..	—	—	—	16	—	17	6	55	—	—	—	6
Women ..	—	—	—	—	—	7	6	13	—	—	—	—
Total ..	—	—	—	16	—	24	12	68	—	—	—	6
Percentage	—	—	—	12·7	—	19·0	9·5	54·0	—	—	—	4·8

TABLE VII.—*Variations from Control of 104 Cases of Combined Duodenal and Lesser-curvature Gastric Ulcer*

	AB	A	B	O
Numbers ..	—	24	12	68
Percentage ..	—	23·1	11·5	65·4
Variation from control	—	−44·0%	+36·5%	+38·2%

there is an increased percentage of group O over the controls of 38.2% but a decrease of 44.0% in group A if the gastric ulcer is on the lesser curve (Table VII). Both of these findings are statistically significant at the 1% level ($p<0.01$). It is remarkable and highly significant that all 16 cases of combined duodenal and prepyloric ulceration came from group O, compared with less than half (47.36%) of the control cases ($p<0.01$). The fact that all six of the patients with duodenal and greater curvature ulcers came from group O is also significant ($p<0.05$). The accompanying diagram shows the percentages of groups A and O in relation to duodenal, prepyloric, and lesser-curvature gastric ulcer.

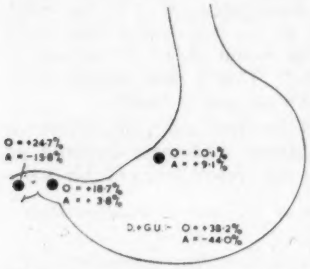

Diagram showing the variations from control of blood groups A and O in duodenal, prepyloric, lesser curvature, and combined duodenal and gastric ulceration.

TABLE VIII.—*Blood-group Percentages of the Duodenal Ulcer Patients of Aird et al.* (1954) *and Køster et al.* (1955) *Compared with the Present Series*

	A	O
Aird *et al.* (1954)	34·67	55·4
Køster *et al.* (1955)	38·4	50·2
Grahame (1960)	34·76	59·0

Table VIII compares the percentages of duodenal ulcer cases in the present series with those of Aird *et al.* (1954) and Køster *et al.* (1955).

Conclusion

There is a significant liability of persons with group O blood to duodenal ulceration and a decreased risk of group A people to this malady.

There would appear to be an increased but not statistically significant risk of group O patients to prepyloric ulceration, but there is not a decreased risk on the part of those with group A blood.

There is no alteration in the risk of group O patients to lesser-curvature gastric ulcer, but there is a small but not significant increase on the part of group A patients. These last findings are the opposite to those of Balme and Jennings (1957), but are in agreement with those of Clarke *et al.* (1955).

There is a remarkably significant decreased risk of group B patients to lesser-curvature gastric ulcer, but the risk to group AB persons is increased.

There is a definitely increased risk on the part of group O patients to combined duodenal and gastric ulceration but a marked decrease in the risk to those with group A blood, and this phenomenon occurs at all three main sites of gastric ulcer.

The risk of group O patients to peptic ulceration diminishes from the duodenum proximally up the stomach, and the risk of group A patients increases, but not to the same extent. Neither of these trends is statistically significant, however; Doll *et al.* (1960), however, showed the same results but did not comment on them.

The decreased risk in group O patients to gastric ulcer compared with the risk to duodenal ulcer does not occur if the patient has already had a duodenal ulcer—in fact, it might increase the risk.

The results support the view that duodenal and gastric ulcers are different diseases except when the two are combined in the same patient. In these circumstances the mechanism may follow the duodenal type.

It is not suggested that all group O patients are liable to duodenal ulcer or that group A patients are protected, because one would expect far greater numbers of peptic ulcer patients than even the most alarming of figures suggest. On the other hand, there could be a hereditary factor at work in some of these patients as one of the causes of ulceration. Again, it must be considered that home and environmental influences may be of greater importance in a family where the patients may be all of one blood group, so that the true hereditary factor may be of minor, if not negligible, proportions.

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REFERENCES

Aird, I., Bentall, H. H., Mehigan, J. A., and Roberts, J. A. F. (1954). *Brit. med. J.*, **2**, 315.
Balme, R. H., and Jennings, D. (1957). *Lancet*, **1**, 1219.
Clarke, C. A., Cowan, W. K., Edwards, J. W., Howel-Evans, A. W., McConnell, R. B., Woodrow, J. C., and Sheppard, P. M. (1955). *Brit. med. J.*, **2**, 643.
Doll, R., Swynnerton, B. F., and Newell, A. C. (1960). *Gut*, **1**, 31.
Køster, K. H., Sindrup, E., and Seele, V. (1955). *Lancet*, **2**, 52.
Roberts, J. A. F. (1953). *Heredity*, **7**, 361.
—— (1957). *Brit. J. prev. soc. Med.*, **11**, 107.

"Research in mental health and mental illness remains none the less under the influence of the vicious circle to which reference has often been made in the reports and at the annual meetings of the Fund. Past neglect and the continuing difficulty of the subject, the competing demands both of clinical psychiatric posts and of research posts in other fields, limit the flow of well-qualified research workers to the relatively few places in the country where effective research is being done; and the limitation of these centres where alone training in psychiatric research can be had limits in its turn the flow on which their own expansion depends. Institutions abroad compete for such workers as emerge and offer them in abundance the facilities and the established posts which are so scarce in this country. . . . The position is complicated by the fact that responsibility for State-financed medical research is shared by three different Ministers of State—the Minister for Science, who is now responsible for the Medical Research Council; the Chancellor of the Exchequer, who is responsible for the University Grants Committee; and the Minister of Health, who is responsible for the National Health Service. However good may be the liaison between these Ministers and between the semi-autonomous bodies for which they are answerable, it would be a powerful encouragement both to the profession and to the bodies concerned if the Government, as a contribution to World Mental Health Year, would announce its intention to develop research into mental health and mental illness and to establish an adequate structure of permanent posts to provide a reasonable career for those wishing to devote themselves to research in psychiatry." (*Annual Report 1959–60*, Mental Health Research Fund.)

FURTHER STUDIES ON THE RECOVERY OF THYROID FUNCTION IN NON-ENDEMIC GOITROUS CRETINISM

BY

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As previously reported, we have been able, through the short-term administration of unphysiologically large doses of thyroid substances, temporarily to return to normal disturbed thyroid function in two siblings who suffered from sporadic goitrous cretinism due to genetically determined enzymatic defects (Zondek *et al.*, 1958, 1959, 1960a, 1960b). As a result of this "stoss-therapy" both patients remained perfectly euthyroid for the next six to seven months without further treatment. Their hitherto very voluminous, partially diffuse and partially nodular goitres remained greatly reduced or virtually absent during these periods.

Investigations of thyroid function performed before treatment revealed a steep rise of thyroidal ^{131}I uptake to abnormally high values during the first two hours followed by a gradual drop to abnormally low values at 24 and 48 hours. This pattern, together with the low serum protein-bound iodine (P.B.^{127}I) found in both siblings, is suggestive of an inability of the thyroid gland to hold and utilize the trapped iodide—that is, of a metabolic block involving the first stages of hormone synthesis. In contrast, the uptake curves showed in one sib a practically normal pattern three and four months after stosstherapy and, in the other, elevated values three weeks and two months after stosstherapy.

The third affected sib came under our observation about a year and a half ago. Our purpose is to report the results of stosstherapy in this patient, special stress being laid on serial investigations of thyroid function performed on a more extensive scale than in the other two sibs.

Case Report

The patient, a man aged 24, was one of a family of nine sibs, two more of whom were similarly affected. He had been given thyroid therapy only sporadically in the past and had had none during the last three years. On admission he was as severely myxoedematous as the other two affected sibs when first seen by us. He was of small stature (1.51 m.) and his appearance and behaviour were characteristic of myxoedema. The face was puffy, the skin dry and wrinkled, the voice hoarse, and the speech and general responsiveness were slow and sluggish. The pulse rate was 56–60 per minute, the heart shadow was somewhat enlarged to the left, and the Achilles tendon reflexes were sluggish. The basal metabolic rate was −34%, and serum cholesterol was 230 mg./100 ml. The patient had a large goitre in which three nodules the size of large walnuts were imbedded. The serum P.B.^{127}I was less than 0.75 μg./100 ml., and thyroidal ^{131}I uptake followed exactly the same pattern as in investigations previously undertaken in his two sibs (first line of Table). Previous examinations at another hospital had revealed an identical uptake pattern, and, moreover, a practically complete discharge of the trapped iodide by potassium thiocyanate (Steinberg and Czerniak, 1955).

The patient was given stosstherapy in the same manner as his two sibs (90 mg. of "triac" within nine days), and he also became free from goitre—with the exception of a small remnant the size of a hazel-nut in the middle lobe—and clinically in every respect euthyroid, the symptoms and signs described above having fully regressed in the course of treatment. The B.M.R. was −9% on the last day of therapy, and rose to ±0 seven days later. The patient has remained euthyroid and virtually free from goitre up to the time of writing—that is, 18 months after stosstherapy was discontinued (see Figs.).

As regards thyroid function, the following data seem pertinent. During stosstherapy the two-hour uptake was, as expected, largely suppressed. The 24-hour uptake was, however, only slightly lower, and the 48-hour uptake was even somewhat higher than the corresponding values in the

Serial Investigations in Case of Familial Sporadic Cretinism with Goitre Before, During, and After 90 mg. of Triac

	Clinical State	B.M.R. %	Goitre	Serum P.B.^{127}I μg./100 ml.*	Thyroidal ^{131}I Uptake (% of Dose)†						
					2 hr.	4 hr.	24 hr.	48 hr.	72 hr.	96 hr.	148 hr.
Before treatment	Myxoedema	−34	+++	<0·75	60		30	15			
During "			++		9·1	12·5	21·1	22·8			
4 days after ..	Euthyroid	−12	±	3·2	28·8		63·8	66			
1 month after ..	"	+9·5	±	6·1	15	17·2	34·2	30·2			
3 months after	"	−6	±	3·7	11·8	18·5	25·0	28·5			
6 " "	"	−10	±	3·2	32	53·5	90	52	50	48·5	41
7½ " "	"	+4	±		36	51	52·5	46	35	32	
9 " "	"	±0	±		61·6		55·5	46·6		37·5	33·6

	Urinary Excretion (% of Dose)		Total Plasma ^{131}I (% of Dose/l.)					P.B.^{131}I (% of Dose/l.)					Non-butanol-soluble ^{131}I (% of Dose/l.)			
	24 hr.	48 hr.	24 hr.	48 hr.	72 hr.	96 hr.	148 hr.	24 hr.	48 hr.	72 hr.	96 hr.	148 hr.	24 hr.	48 hr.	96 hr.	148 hr.
Before treatment		14·0	1·6													
During "	54·5	8·2	0·88	0·2				0·08	0·06							
4 days after ..	41·5	5·5	0·96					0·37								
1 month after ..		6·0	0·52					0·05								
3 months after ..	44·5	3·2	0·32					0·05								
6 " " ..	6·9	3·2	0·36	0·56				0·19	0·43				0·041	0·09		
7½ " " ..	19·5		0·76	0·88	1·16	1·4		0·37	0·56	1·0	0·86					
9 " " ..	17·5	9·4	1·7	1·2		1·8	1·8	1·05	0·83		1·44	1·6	0·12	0·15	0·31	0·28

* Normal range: 3·5–5·5 μg./100 ml. † With the exception of the last examination, when 300 μc. was given, 50 μc. ^{131}I was administered by the oral route.

untreated state. The conversion ratio was low (second line of Table), yet it is evident that the gland was already to some extent able to bind elementary iodine to protein. Five to seven days after the withdrawal of therapy, ^{131}I uptake was surprisingly high, while the conversion ratio was

Patient, aged 24, with familial sporadic cretinism with goitre. Left: Before treatment. Right: Same patient seventeen months after "stosstherapy."

normal (third line of Table). One month and three months after stosstherapy thyroid function was in the low normal range, or, as regards iodine binding, even below normal (fourth and fifth lines of Table).

This almost induced us to believe that the patient's thyroid gland, unlike those of his younger brother and sister, would lose its functional capacity at a comparatively early date. However, to our surprise, tracer studies performed at six, seven and a half, and nine months after stosstherapy (sixth to eighth lines of Table) revealed an abnormally active pattern which was maintained during observation periods ranging up to seven days as regards both iodine uptake and the formation and release of a P.B.I. compound into the circulation. The urinary excretion of ^{131}I did not always conform to the uptake and conversion values, being at times even at variance with either or both of them (see, for example, the last line of Table). Total plasma ^{131}I activity was uniformly high during the whole period of observation and there was a distinct tendency towards its continuous rise during the two extended observation periods at seven and a half and nine months after stosstherapy. The serum P.B.^{127}I was at the lower range throughout the whole period of observation with the exception of one value above the upper normal limit. The butanol-insoluble fraction of the circulating iodine compound, which was determined only during the later stages of the remission, ranged, with the exception of one value, between 11 and 17%, as compared with normal values of 5 to 8% for our laboratory. The presence of thyroxine in the butanol-soluble fraction nine months after the triac stoss was demonstrated by paper chromatography performed with the ascending technique, using butanol-dioxane-ammonia (Gross, 1954); the chromatograms revealed definite evidence of thyroxine 24 and 48 hours after the ingestion of ^{131}I; however, for technical reasons the exact amounts could not be determined. The nature of other iodine compound(s) in the chromatograms could also not be determined.

Discussion

The foregoing data demonstrate again that unphysiological quantities of thyroid substances—that is, quantities considerably greater than the amount produced daily by the thyroid and required by the organism—can induce functional recovery of the genetically diseased thyroid gland of goitrous cretins, and a prolonged clinical remission lasting in the case presented here so far for 18 months. In the two other affected siblings the same therapeutic procedure (stosstherapy) had also resulted in long-standing remissions, which, however, on no occasion exceeded seven months. In these two the functional state of the thyroid gland had been investigated only during the first half of the therapy-free remissions, while in the present case tracer studies were performed during both the early and the later stages of the remission.

Irrespective of the clinical state, we can distinguish in this patient three phases of thyroid activity induced by stosstherapy: (1) immediately after its discontinuation, a rise; (2) one month and three months later, a drop to the low normal range; and (3) at six, seven and a half, and nine months after stosstherapy, an even greater rise simulating in some respects genuine hyperfunction. At any rate ample evidence is provided by our investigations that—especially during the later stages of the remission—the thyroid was rendered not only capable of holding large amounts of iodine but also of forming therefrom P.B.I. and of releasing it into the circulation. The fact that the patient remained euthyroid and practically agoitrous indicates that at least part of the material was biologically active. This assumption was borne out by the chromatographic separation of the circulating iodine compound which revealed the presence of thyroxine in amounts which, in view of both the clinical state and the increase of the serum P.B.I. content, may be safely assumed to exceed those secreted in the pre-treatment period. This finding must be regarded as the crucial observation of the whole laboratory investigation.

The inconsistencies in this study—for example, the lack of correlation between ^{131}I uptake and excretion, or between the serum P.B.^{127}I and P.B.^{131}I—are as yet unexplained. Besides an increased re-utilization of iodine in the thyroid, an abnormal turnover of thyroid hormone in the peripheral tissues may be postulated. This will be the subject of further investigations.

The observation that in this patient (as also in the other two affected sibs) large doses of active thyroid substances failed to produce the practically complete suppression of thyroid activity which we are accustomed to find in nearly all conditions other than present and past hyperthyroidism may also be added to the list of notable findings in this group of patients.

We are not in a position to state with certainty in what way the at least partial correction of the genetically transmitted enzymatic defect of thyroid hormone synthesis was brought about. Nevertheless, we think as already suggested in previous communications (Zondek *et al.*, 1958, 1959, 1960b) that the end-product of thyroid secretion, if administered in doses exceeding the physiological range, may restore to normal a disturbed interaction between thyroid enzymes and the hormone-producing cell particles, thus setting in motion an intracellular mechanism regulating thyroid secretion.

Summary

The case is presented of a 24-year-old familial sporadic cretin with goitre in whom thyroid deficiency was due to a genetically transmitted inability of the gland to hold and utilize the trapped iodide. The short-term administration of unphysiologically large doses of thyroid substances produced in this patient a clinical remission with almost complete regression of the goitre which has so far lasted for one and a half years.

(Similar remissions, though of shorter duration, had previously been achieved with both triac and desiccated thyroid in two similarly affected sibs.)

Thyroid function was investigated during "stoss-therapy" and during both the early and the late stages of the remission. During stosstherapy thyroid activity was suppressed only at two hours after the administration of the tracer, but not at 24 and 48 hours. Immediately after the discontinuation of stosstherapy there was a hyperactive uptake pattern; one and three months later, a low-normal; and six, seven and a half, and nine months later a hyperactive pattern as to ^{131}I uptake, total activity, and conversion which was manifest during observation periods ranging up to seven days. The butanol-soluble fraction of the circulating ^{131}I compounds was somewhat lower than normal. Its chromatographic separation nine months after stoss-therapy revealed the presence of thyroxine and of another, as yet undefined, iodine compound(s). The serum P.B.^{127}I was, with one exception, at the lower limit of the normal range throughout the whole course of observation.

The implications of these observations are discussed. It is suggested that the end-product of thyroid secretion, if administered in amounts exceeding the physiological range, induces a recovery of thyroid function by correcting a genetically disordered interaction between intracellular thyroid enzymes and hormone-producing cell particles (thyroidal autoregulation).

Our thanks are due to Dr. H. M. Walker, Glaxo Laboratories Ltd., Greenford, Middlesex, for the generous supply of triac. We are indebted to the Department of Biochemistry, to E. Wertheimer, Hebrew University Hadassah Medical School, Jerusalem, for the serum P.B.^{127}I determinations, and to Miss Sara Kornitzer for technical assistance.

REFERENCES

Gross, J. (1954). *Brit. med. Bull.*, **10**, 218.
Steinberg, A., and Czerniak, P. (1955). *Harefuah*, **48**, 12.
Zondek, H., Leszynsky, H. E., and Zondek, G. W. (1958). *Acta endocr. (Kbh.)*, **29**, 47.
—— —— —— (1959). *Brit. med. J.*, **1**, 340.
—— —— —— (1960a). *Arch intern. Med.*, **106**, 15.
—— —— and Stein, J. A. (1960b). *Nature (Lond.)*, **187**, 515.

"A noticeable change in the last ten years [in the general medical, haematological, endocrinological, and mental observation departments] is the increasing number of coloured people both in wards and out-patients; their diseases generally differ little from European illnesses except that they are occasionally infested with hookworm and so develop its resultant anaemia (a condition which can be easy to miss when their pallor is masked by their pigment). As a community they have a smaller number of old people than we do. The old people stay in the West Indies, while the young come to earn better money in England. Family feeling seems strong, and many regular payments are posted back home by those working here. As patients, they are shy and often suspicious, and their speech is so different from ordinary English that the exchange of ideas is slower and less accurate than with English patients. For these reasons West Indians sometimes appear to be moody, morose or ungrateful as patients when they are really embarrassed and fearful. Because their standard of education is lower, instructions like measuring insulin or adhering to particular articles of food are harder to explain. Although their homes are mostly of a lower standard than the average European, their health does not seem to be affected by this except that they have to be taken to hospital for minor illnesses which otherwise might have been managed at home." (Dr. Richard Asher in *Central Middlesex Hospital Annual Report, 1959.*)

THYROID FUNCTION IN THE EUTHYROID PARENTS OF THREE NON-ENDEMIC GOITROUS CRETINS

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We have under observation three siblings with goitrous cretinism who were born and reared in Israel, a comparatively goitre-free region. They are the fourth, fifth, and eighth of nine children, the other six being clinically healthy. Both parents come from Iraq, from allegedly healthy, unrelated families.

The purpose of this paper is to report the results of tracer studies in the parents. Observations on the affected offspring have been reported elsewhere (Zondek *et al.*, 1958, 1959, 1960a, 1960b, 1961).

The father, aged 62, is healthy and has no complaints. He is clinically euthyroid, and the thyroid gland was normal on palpation. The B.M.R. was +3%, and the serum cholesterol 210 mg./100 ml.

FIG. 1.—Clinically euthyroid mother, aged 50, of three non-endemic goitrous cretins.

His serum protein-bound iodine (P.B.^{127}I) was 3.4 μg./100 ml. (normal range, 3.5–5.5 μg./100 ml.), and tracer studies revealed perfectly normal values with regard to both uptake and conversion of ^{131}I; thyroidal uptake was 12.2% at two hours, 20% at four hours, 39% at 24 hours, and 37% at 48 hours. The conversion ratio was 35% at 24 hours and 46% at 48 hours.

The mother, aged 50, at first sight has endocrine stigmata: she is of small stature (1.44 m.), is fat (50 kg.), and mentally dull, and she has a cretinoid appearance, with narrow palpebral fissures and a depressed root of the nose (Fig. 1). The thyroid gland is normal to palpation except for a very small nodule in the middle lobe.

From the clinical viewpoint the mother's thyroid function was found normal in all respects: B.M.R., −2%; serum cholesterol, 226 mg./100 ml.; heart function and configuration normal; E.C.G., normal. The serum P.B.^{127}I was 4 μg./100 ml. Twice-repeated tracer studies (see Table and Fig. 2) revealed

a high thyroidal uptake of ^{131}I which remained practically steady during the four days of observation, with a correspondingly low urinary excretion of the tracer. During the first two days the total plasma activity was in the low normal range, but, instead of decreasing further, it rose steadily to abnormally high values during the next two days. The conversion ratio was high normal to high. The percentage of the butanol-insoluble fraction was abnormally high throughout. A paper chromatographic separation of the circulating iodine compounds at 24, 48, 72, and 96 hours, performed by the ascending technique with butanol-dioxane-ammonia (Gross, 1954), gave normal results.

Investigations in Clinically Euthyroid Mother of Non-endemic Goitrous Cretins

	Total Plasma ^{131}I (% of Dose/l.)	P.B.^{131}I (% of Dose/l.)	Non-butanol-soluble ^{131}I (% of Dose/l.)
24 hr. ..	0·1	0·068	0·033
48 ,, ..	0·1	0·066	0·021
72 ,, ..	0·19	0·184	0·054
96 ,, ..	0·26	0·255	0·066

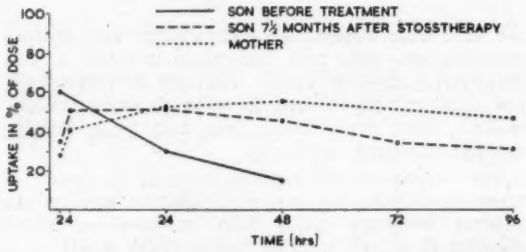

FIG. 2.—Thyroidal ^{131}I uptake curves of mother and son.

Conclusion and Summary

Tracer studies with ^{131}I revealed in the clinically euthyroid but, on appearances, cretinoid mother of three goitrous cretins the following abnormalities: a high thyroidal uptake which hardly decreased during two observation periods of four days each, with a correspondingly low urinary excretion, a steady increase of total plasma activity during the same time, a high normal to high conversion ratio, and an abnormally low butanol solubility of the circulating iodine compounds.

These findings are in surprising agreement with the results of corresponding studies in one of her affected offspring performed at six, seven and a half, and nine months of a therapy-free remission which was induced by the short-term administration of unphysiologically large quantities of thyroid substances (Zondek *et al.*, 1961). Although some qualitative and quantitative differences are apparent, the general trend is the same in the permanently and endogenously euthyroid mother and in the son whose severely disordered thyroid function was set in motion by the above-described "stosstherapy."

A similar uptake pattern was also evident in the other two affected and similarly treated sibs during their remissions (Zondek *et al.*, 1958, 1959).

REFERENCES
Gross, J. (1954). *Brit. med. Bull.*, **10**, 218.
Zondek, H., Leszynsky, H. E., and Zondek, G. W. (1958). *Acta endocr. (Kbh.)*, **29**, 47.
—— —— —— (1959). *Brit. med. J.*, **1**, 340.
—— —— —— (1960a). *Arch. intern. Med.*, **106**, 15.
—— —— and Stein, J. A. (1960b). *Nature (Lond.)*, **187**, 515.
—— —— Zondek, G. W., Stein, J. A., and Guttmann, S. (1961). *Brit. med. J.*, **1**, 97.

PUNCH BIOPSY OF THE PERITONEUM

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DeFrancis *et al.* (1955) described a technique, using the Vim Silverman needle, for obtaining parietal pleural biopsy in pleural effusion. Donohoe *et al.* (1959) applied a similar approach to the study of patients with intra-abdominal disease with ascites. They described a technique, also using Vim Silverman needle, for obtaining peritoneal tissue in cases of ascites.

In our hospital we have used the Harefield pleural punch biopsy needle (Fig. 1), devised by Leon D. Abrams (1958), which enabled us to perform paracentesis of the ascitic fluid and punch biopsy of the

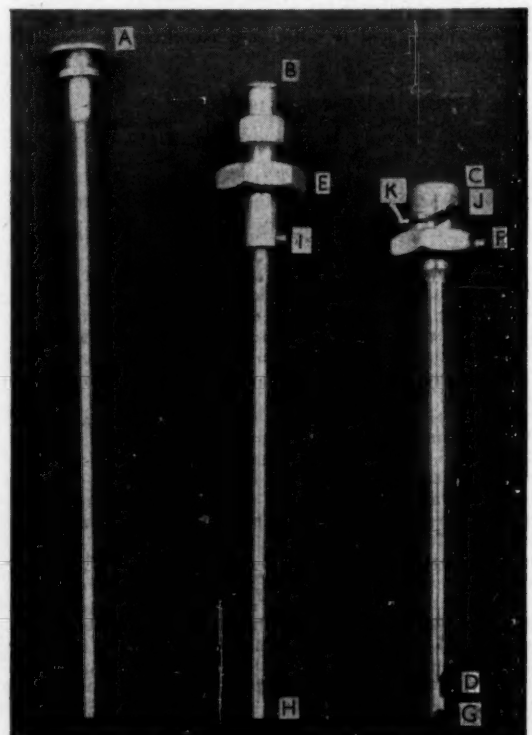

FIG. 1.—Abram's needle. A, Stylet; B, Inner concentric tube; C, Outer concentric tube; D, Notch; E, Back hexagonal grip; F, Knob; G, Trocar point; H, Cutting edge; I, Pin; J, Oblique slot; K, Spring clip to hold pin.

peritoneum in one operation. The technique, its indications and limitations, and the results, together with some case reports, form the basis of this report.

Technique

The patient is placed in the position used for routine paracentesis. The site chosen is prepared in the usual manner. The skin and subcutaneous tissue down to the peritoneum is infiltrated with 1% procaine hydrochloride. A tiny transverse incision is made in the skin, and the punch is introduced with the notch closed and the stylet in position. At this stage the patient is encouraged to increase intra-abdominal pressure further. The stylet is removed after entering the peritoneal cavity and the back hexagonal grip is twisted anticlockwise to open the notch. Ascitic fluid is collected for physical, chemical, cytological, and bacteriological examinations. After the collection of ascitic fluid the punch is slowly withdrawn until the fluid just ceases or just trickles. This theoretically places the edge of the notch at the level of the peritoneum. The punch is then held firmly against the abdominal wall, the back hexagonal grip twisted sharply clockwise, and the punch withdrawn. Finger pressure for two or three minutes stops any bleeding from the puncture. The biopsy specimen is found either in the hollow point or inside the cutting cylinder.

Results

Punch biopsy of the peritoneum was performed in 23 cases. An adequate specimen of the peritoneal tissue could be obtained in 21 out of 25 attempts. Failure to obtain a specimen occurred in patients having minimal ascites, in whom no fluid was obtained during the puncture. The failure in these cases could be ascribed to the difficulty of locating by puncture the level of peritoneum in the absence of fluid. Figs. 2–4 show sections of tissue obtained by punch biopsy of the peritoneum.

No complications were encountered in any patient.

The accompanying Table summarizes the results obtained in all cases.

Provisional Clinical Diagnosis	No. of Cases	No. of Biopsy Attempts	No. of Cases in which Adequate Peritoneal Tissue was Obtained	Results and Remarks
Cirrhosis of liver	7	8	7	4 had congestion of vessels and mesothelial hyperplasia. 1 had congestion of vessels. 1 had normal peritoneal tissue. 1 had A.F.B. lesion
Tuberculous abdomen	8	9	6	Histological confirmation of diagnosis made in 3. Normal in 3. Failure to obtain specimen in 2
Congestive heart failure (cor pulmonale)	3	3	3	All specimens had non-specific changes—viz., dilatation and marked congestion of vessels
Peritoneal metastases	2	2	2	Histological confirmation of metastases in peritoneum obtained in both cases
Budd–Chiari syndrome	1	1	1	Normal peritoneum
Ascites of unknown aetiology	1	1	1	A.F.B. lesion demonstrated in peritoneal tissue, thus enabling diagnosis of tuberculous peritonitis in case presenting with ascites, hepatomegaly, and anaemia
Amyloidosis ..	1	1	1	Normal peritoneum

Case Reports

Case 1.—A Hindu woman aged 50 was admitted to hospital complaining of abdominal pain and distension, anorexia, and loss of weight for the previous 10 weeks. Her history did not contain anything significant. Physical examination revealed massive ascites, and a firm, non-tender, smooth mass could be palpated in the posterior fornix of the vagina. Nothing abnormal was detected in the rest of the systemic examination. Laboratory examination: the blood, urine, stool, and liver-function tests were within normal limits, except an elevated blood sedimentation

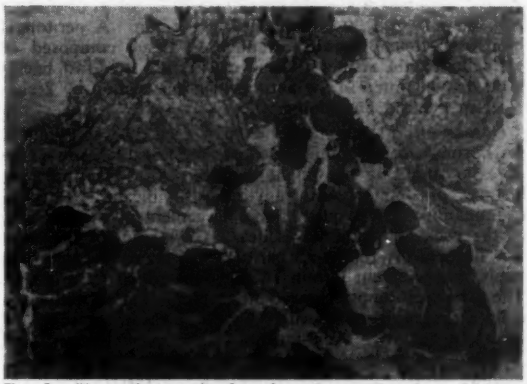

FIG. 2.—Photomicrograph of section of normal peritoneal biopsy showing thin mesothelial lining, underlying connective tissue, and muscle fibres. (H. and E. ×80.)

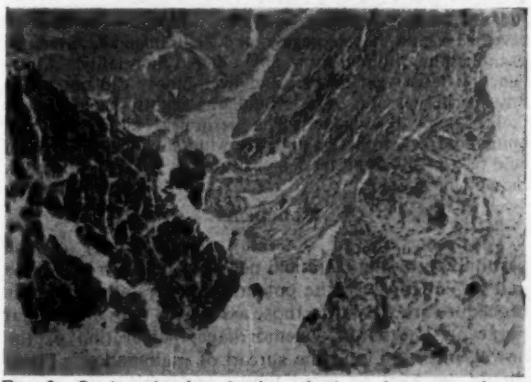

FIG. 3.—Section showing deeply stained carcinomatous tissue, seen at lower left corner of photomicrograph, obtained by percutaneous peritoneal biopsy. (H. and E. ×80.)

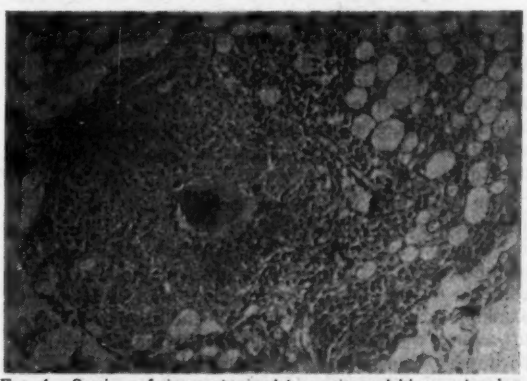

FIG. 4.—Section of tissue obtained by peritoneal biopsy showing tuberculous granulation tissue. Acid-fast bacilli were seen on staining by Ziehl-Neelsen method. (H. and E. ×100.)

rate (90 mm./hour, Westergren). Ascitic fluid was haemorrhagic, having a specific gravity of 1016 and 2.4 g. of protein per 100 ml.; cytological examination by Papanicolaou's technique revealed class I cells. Peritoneal biopsy disclosed an anaplastic malignant growth, some cells showing evidence of mucus secretion.

Case 2.—A Hindu man aged 25 was admitted to hospital complaining of distension of the abdomen and anorexia for two months. His previous history did not reveal anything significant. Liver-function tests were slightly abnormal (T.T. 4 units, T.F. +) and the liver biopsy obtained by Vim Silverman needle confirmed the diagnosis of portal cirrhosis. Ascitic fluid had a specific gravity of 1020, 5.1 g. of protein per 100 ml., and 20 lymphocytes per c.mm. A peritoneal biopsy specimen revealed granulation tissue composed of epithelioid cells, giant cells, and caseation. Acid-fast bacilli were demonstrated in the peritoneal tissue section by Ziehl-Neelsen method of staining.

Case 3.—A Mohammedan woman aged 20 was admitted to hospital complaining of loss of appetite, low-grade pyrexia, and loss of weight for 25 days. Her previous history did not reveal anything significant. Physical examination showed glandular enlargement in the left side of the neck and minimal ascites. A skiagram of the chest was normal. A follow-up barium-meal study revealed ileal stasis, and adherent terminal ileal loops which were tender. The peritoneal biopsy showed an accumulation of epithelioid cells arranged in a follicular pattern and the presence of caseation necrosis. Acid-fast bacilli could be demonstrated in the peritoneal tissue by the Ziehl-Neelsen method of staining.

Case 4.—A Hindu woman aged 30 was admitted to hospital complaining of distension of the abdomen and weakness for two and a half months. Her previous history did not contain anything significant. Physical examination revealed ascites, hepatomegaly, and slight anaemia. Systemic examination did not show any other abnormality. Liver-function tests were normal and liver biopsy did not reveal any specific disease. Ascitic fluid was slightly haemorrhagic and probably exudative. The peritoneal biopsy revealed epithelioid cell follicles, some showing slight caseation, and acid-fast bacilli could be demonstrated by the Ziehl-Neelsen method of staining.

Comments

The procedure of obtaining punch biopsy of the peritoneum by the Harefield needle appears to be simple and safe. However, the potential dangers attending this procedure are similar to those associated with abdominal paracentesis—that is, haemorrhage, perforation of the bowel, infection, and the spread of malignancy. These should be kept in mind while performing the punch biopsy of peritoneum.

Peritoneal biopsy confirmed the diagnosis in three out of six clinically suspected cases of tuberculous abdomen, and it enabled the diagnosis of tuberculous peritonitis to be made in two unsuspected cases presenting with portal cirrhosis (Case 2) and ascites (Case 4). It is felt that peritoneal biopsy may provide an important tool for making a firm diagnosis of tuberculous peritonitis where other conventional methods usually are inadequate.

The procedure was found useful in investigation of the cases presenting with ascites. It is best exemplified in Case 4, where peritoneal biopsy clinched the diagnosis of tuberculous peritonitis when other methods—namely, clinical, ascitic fluid, liver-function, and liver biopsy examinations—failed to establish the diagnosis. The procedure was also found useful in the diagnosis of peritoneal metastases. The limitations of this procedure should, however, be borne in mind. Firstly, as in other punch biopsies, peritoneal biopsy can only reflect the histological changes demonstrable in the focal area from which the biopsy is obtained, and hence false-negative results may be obtained. Secondly, the serous membranes often reflect no histological changes or those of a non-specific nature when involvement of membrane *per se* either does not exist or is not diffuse.

Our preliminary experience suggests that needle biopsy of the peritoneum often provides a rapid and accurate diagnosis, sometimes when other methods have failed, and in combination with other routine laboratory investigations may allow a firm diagnosis to be made in a larger number of cases presenting with ascites than would otherwise be possible.

Summary and Conclusions

Twenty-three patients with varying disease and ascites were subjected to punch biopsy of the peritoneum, using the Harefield needle.

The procedure is simple and safe. An adequate specimen of the peritoneal tissue could be obtained in 84% of cases. Failure to obtain an adequate tisue was observed in cases having minimal ascites, in which no fluid was obtained during the puncture.

No complications were encountered in any patient.

Our preliminary impressions suggest that the procedure is useful in investigation of ascites and tuberculous abdomen with peritoneal involvement, and in the diagnosis of peritoneal metastases.

REFERENCES

Abrams, L. D. (1958). *Lancet*, **1**, 30.
DeFrancis, N., Klosk, E., and Albano, E. (1955). *New Engl. J. Med.*, **252**, 948.
Donohoe, R. F., Shnider, B. I., and Gorman, J. (1959). *A.M.A. Arch. Intern. Med.*, **103**, 739.

CARDIOMEGALY IN A NEWBORN DUE TO PLACENTAL CHORIOANGIOMA

BY

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Enlargement of the heart resulting from a high cardiac output may be caused by abnormal arteriovenous communications (Holman, 1923; Cohen *et al.*, 1948; Wood, 1956). We describe the case of a newborn infant in whom cardiac enlargement was probably caused by a vascular shunt through a large placental chorioangioma.

Case Report

The mother was 33 years of age and in good health; she had had four normal full-term infants and two abortions. Routine antenatal care for the present pregnancy began at the nineteenth week of gestation. At this time she had no symptoms, physical examination was negative, the height of the fundus uteri was compatible with 18 weeks' gestation, and her blood-pressure was 100/66. Her haemoglobin was 12.6 g./100 ml. (81%), and her urine was free from albumin and sugar. Foetal movements were first noticed at 22 weeks of pregnancy. She was perfectly well when seen at the 24th and 29th weeks. At 31 weeks and again eight days later

she complained of vomiting, heartburn, and a dry cough. At this time the height of the fundus was excessive for the stage of pregnancy, and hydramnios was suspected. No other abnormality was noted, and she was advised to rest. Promethazine theoclate ("avomine"), 25 mg. eight-hourly, was prescribed. However, next day she went into labour and was admitted to hospital at the 32nd week.

The first stage of labour lasted nine hours. As the membranes were still intact after full dilatation of the cervix, artificial rupture was performed, but only a small amount of meconium-stained liquor escaped. The vertex presented, and after a second stage of 20 minutes a female infant, 3 lb. (1,360 g.) in weight, was delivered. The clinical impression of hydramnios was confirmed by the large volume of amniotic fluid which was forcibly ejected from the uterus during delivery of the infant, although it could not be collected for measurement. The umbilical cord was clamped and tied immediately after delivery, the infant being at the same horizontal level as the placenta, which was delivered 10 minutes later. Light "trilene" inhalation anaesthesia was administered to the mother only during delivery of the head.

The infant cried immediately after birth and her general condition was good. Multiple petechiae were present on the head, face, and neck, but physical examination was otherwise negative. The pharynx was aspirated with a mucus catheter, and the infant was placed in an incubator at a temperature of 90° F. (32.2° C.) and humidity of 75% with an oxygen flow of 1 to 2 litres per minute. "Synkavit" (vitamin K analogue) 1 mg. was given intramuscularly. A few minutes after birth respirations were rapid and costal recession was noted, and at about three hours grunting began. Generalized oedema was evident by the eighth hour. At 14 hours the costal recession and grunting respirations were more pronounced and the respiratory rate was 80 per minute. The percussion note over the lungs was resonant and normal breath sounds were present. There were no adventitious sounds. The liver was uniformly enlarged to 3 cm. below the right costal margin and the spleen was felt 1 cm. below the left costal margin. There were no cardiac murmurs. The tension of the anterior fontanelle was normal. The rectal temperature was 95.6° F. (35.3° C.).

Central cyanosis became evident after the first 24 hours, the respiratory distress increased, and the general condition steadily deteriorated. The size of the liver and spleen remained unaltered. There was a small vomit at 39 hours. Small amounts of sterile water were offered by mouth. Streptomycin, 40 mg. 12-hourly, and crystalline penicillin, 100,000 units six-hourly, were given intramuscularly. Because of the severe respiratory distress a mixture of 79% helium and 21% oxygen was supplied to the incubator, but no improvement resulted, and death occurred at 69 hours.

Six hours before death the urine was free of sugar and albumin, though it contained many epithelial cells and scanty leucocytes, but no casts; culture gave a growth of coagulase-negative *Staphylococcus albus*. A chest *x*-ray film taken five minutes before death showed marked cardiac enlargement and mottled opacities in both lung fields.

Post-mortem Findings

At necropsy (Dr. G. A. K. Missen) the weight was 1,600 g., length 41.3 cm., and head circumference 28.8 cm.

The *placenta* measured 172 by 145 by 50 mm. and weighed 635 g. after formol fixation. The cotyledons were large and appeared pale. A chorioangioma measuring 166 by 100 by 60 mm. and weighing 542 g. after formol fixation was adherent to the maternal aspect of the placenta; a fusiform vessel (3 by 1 cm.) connected the chorioangioma to the umbilical vein (Fig. 1). The chorioangioma was a dark-brown reniform mass, with a smooth lobulated surface. The concave aspect was firmly attached to the maternal surface of the placenta. The cut surface of the chorioangioma showed spherical nodules of varying sizes, separated by a framework of many branching fibrous trabeculae. Microscopically the nodules were seen to be made up of densely packed capillary channels filled with blood and separated from each other by less vascular connective-tissue septa (Figs. 2 and 3). A number of venous channels were also present. In one nodule a focus of necrosis was seen, and in another an area of calcification was present. The umbilical cord appeared normal apart from moderate dilatation of the distal 2.4 cm. of the umbilical vein. It is probable that blood entered the angioma from vascular channels supplied by the placental arteries through its

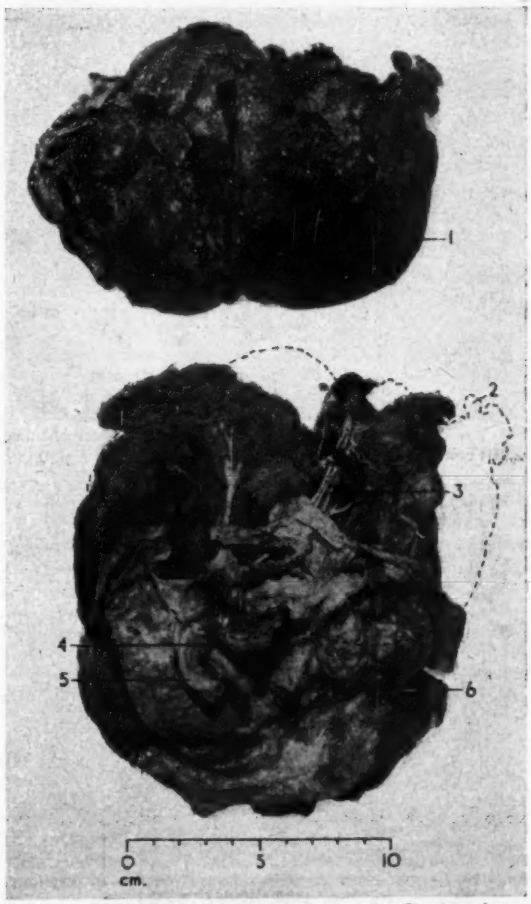

FIG. 1.—Chorioangioma and placenta. 1, Chorioangioma. 2, Outline of chorioangioma, showing original relationship to placenta. 3, Placental arteries feeding tumour. 4, Fusiform dilatation of umbilical vein, draining the chorioangioma. 5, Umbilical cord. 6, Edge of amnion.

surface attached to the maternal aspect of the placenta and returned to the foetus by the large fusiform vessel connecting it to the umbilical vein.

Heart and Great Vessels.—The only abnormality was generalized cardiac enlargement, the heart weighing 21 g.—normal for weight of infant, 10.8 g. (Potter, 1952). This cardiomegaly was due to hypertrophy of all chambers. There was no endocardial fibro-elastosis. The foramen ovale showed a normal valvular aperture. The pericardium, valves, coronary arteries, and main blood-vessels were all normal. The ductus arteriosus was patent and normal in size. Histologically the heart showed hypertrophied muscle fibres as the only abnormality. No excess of glycogen was demonstrated either in periodic-acid–Schiff preparations or by Best's method.

Respiratory System.—The bronchial tree and pleurae were normal. Both lungs appeared well aerated and floated in water, but there were a few foci of haemorrhage up to 3 mm. in diameter, especially in the lingula. Histology showed

changes typical of pulmonary syndrome of the newborn (Bound *et al.*, 1956), consisting of areas of intra-alveolar haemorrhage, atelectasis, and scanty hyaline membrane formation.

The *liver* was uniformly enlarged, weighing 96 g.—average for weight of infant, 66.3 g. (Potter, 1952)—and of a tawny brown changing to deep green with formol fixation. Microscopy showed the canaliculi to contain large numbers of bile

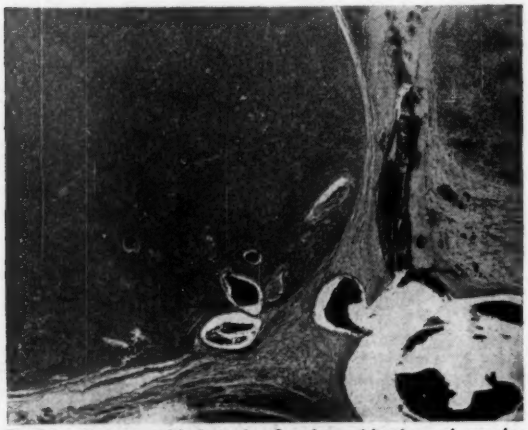

FIG. 2.—Tumour with branch of a large blood-vessel running between two nodules of angiomatous tissue. (H. and E. ×17.)

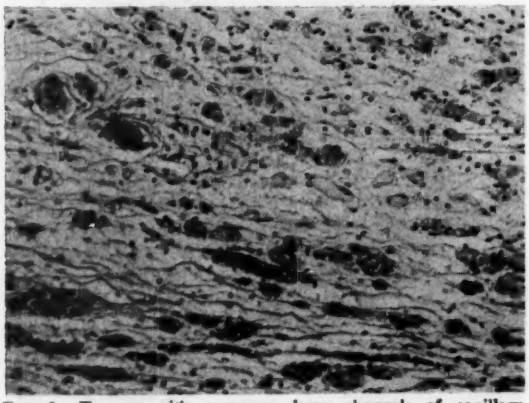

FIG. 3.—Tumour with numerous large channels of capillary structure. (van Gieson. ×375.)

thrombi. Only small amounts of glycogen were demonstrated. The bile ducts were not dissected, but the meconium was of normal colour. The *spleen* was uniformly enlarged, weighing 19 g.—normal for weight of infant, 4 g. (Potter, 1952).

Nervous System.—The meninges and cerebral vessels were normal. The cerebrospinal fluid was slightly xanthochromic. The brain was not swollen, but numerous petechial haemorrhages were scattered throughout the white matter of both cerebral hemispheres. There was no kernicterus.

The remaining systems all appeared normal both to the naked eye and microscopically.

Discussion

The clinical picture and pathological findings at necropsy left little doubt that the cause of death was pulmonary syndrome of the newborn with prematurity. We believe that the cardiac hypertrophy did not contribute to death, since the cause of the hypertrophy —namely, the shunt through the placental angioma—was no longer operative.

Benign tumours of the placenta have been recognized for many years, and John Clarke (1798) reported one of the earliest cases. Since then there have been numerous reports of similar tumours, which, from the description of Beneke (1900), have been classified as chorioangiomata. There have been several reviews, notably those by Siddall (1924), Marchetti (1939), and DeCosta *et al.* (1956). The incidence of chorioangiomata has been variously assessed as 1 in 9,000 (Kühnel, 1933) and 1 in 3,500 (Marchetti, 1939). Hydramnios and prematurity, both of which were present in our patient, have been associated with about one-third of the cases reported. Hydramnios is more often associated with large tumours (Siddall, 1924), and the size of the chorioangioma described in this paper is greater than most of those previously reported. Most authors have considered that the high foetal mortality rate was due to prematurity. However, Siddall (1924) has reported 17 deaths among 73 probably mature infants, and this seems a remarkably high death rate.

Various congenital abnormalities in the infant have been described in association with chorioangiomata, and these have included hydrocephalus (Steinbüchel, 1892), anomalies of the aortic arches (Barry *et al.*, 1951), haemangiomata of the liver (Barry *et al.*, 1951 ; DeCosta *et al.*, 1956), haemangiomata of the skin (Bret *et al.*, 1953), and multiple congenital anomalies (Burger *et al.*, 1952).

The size of the heart has only occasionally been mentioned in reported cases, and we have found no report of cardiac hypertrophy. Cardiomegaly in newborn infants may be due to congenital heart disease, endocardial fibro-elastosis (Potter, 1952), or glycogen disease of the heart (Di Sant'Agnese *et al.*, 1950), and has been seen in newborn infants with cerebral arteriovenous aneurysm (Corrin, 1959 ; A. E. Claireaux, 1960, personal communication). However, there remain a small number of cases of cardiac enlargement in which no cause is evident (Green and Apley, 1950). We suggest that large placental chorioangiomata may be a further and hitherto unrecognized cause of cardiomegaly in the newborn.

Summary

The case of a premature infant with cardiac hypertrophy is reported. A large chorioangioma was attached to the placenta.

Death from pulmonary syndrome of the newborn occurred on the third day.

The heart was normal except for hypertrophy of the muscle fibres.

It is suggested that the cardiac hypertrophy was caused by high cardiac output due to the shunt through the chorioangioma.

We are particularly grateful to Dr. G. A. K. Missen for the full necropsy report and for helpful suggestions. Our thanks are due to Dr. R. C. MacKeith and Dr. R. E. Bonham-Carter for reading the manuscript, to Mr. Blaikely for permission to publish, to the Department of Medical Illustration for Fig. 1, and to Mr. A. N. Finch for Figs. 2 and 3.

REFERENCES

Barry, F. E., McCoy, C. P., and Callahan, W. P., jun. (1951). *Amer. J. Obstet. Gynec.*, **62**, 675.
Beneke, R. (1900). *Verh. dtsch. path. Ges.*, **2**, 407.
Bound, J. P., Butler, N. R., and Spector, W. G. (1956). *Brit. med. J.*, **2**, 1191.
Bret, A. J., Loewe-Lyon, Duperrat, B., and Gauthier, R. (1953). *Presse méd.*, **61**, 1193.

Burger, P., Frühling, L., and Wurch, T. (1952). *Rev. franç. Gynéc.*, **47**, 45.
Clarke, J. (1798). *Philos. Trans. B*, **1**, 361.
Cohen, S. M., Edholm, O. G., Howarth, S., McMichael, J., and Sharpey-Schafer, E. P. (1948). *Clin. Sci.*, **7**, 35.
Corrin, B. (1959). *J. clin. Path.*, **12**, 412.
DeCosta, E. J., Gerbie, A. B., Andresen, R. H., and Gallanis, T. C. (1956). *Obstet. and Gynec.*, **7**, 249.
Di Sant'Agnese, P. A., Andersen, D. H., and Mason, H. H. (1950). *Pediatrics*, **6**, 607.
Green, H., and Apley, J. (1950). *Pediatrics*, **5**, 249.
Holman, E. (1923). *Arch. Surg. (Chicago)*, **7**, 64.
Kühnel, P. (1933). *Acta obstet. gynec. scand.*, **13**, 143.
Marchetti, A. A. (1939). *Surg. Gynec. Obstet.*, **68**, 733.
Potter, E. L. (1952). *Pathology of the Fetus and the Newborn*, pp. 13, 206. Year Book Publishers, Chicago.
Siddall, R. S. (1924). *Amer. J. Obstet. Gynec.*, **8**, 554.
Steinbüchel, R. (1892). *Zbl. Gynäk.*, **16**, 465.
Wood, P. (1956). *Diseases of the Heart and Circulation*, 2nd ed., p. 915. Eyre and Spottiswoode, London.

Preliminary Communications

Optimal Dose of Streptomycin in Pulmonary Tuberculosis

Stradling and Pool (1958) have advocated long-term streptomycin and isoniazid as the most efficient drug combination in tuberculosis. Whether patients will accept this over a long period has yet to be shown, and the question of how to overcome vertigo in elderly patients receiving streptomycin is still unanswered.

In 1958 we began a study which, among other aims, was designed to assess methods of diminishing streptomycin vestibular damage either by using a smaller daily dose of streptomycin or by the addition of pantothenic acid to streptomycin in the normal dose. The following were excluded—non-Europeans, diabetics, expectant mothers, those with evidence of pneumoconiosis, and those who had previous chemotherapy. So far, 135 new patients over the age of 15 suffering from active pulmonary tuberculosis have been accepted. When a patient was admitted to the trial the name was forwarded to a central secretary, who chose a card at random from a series specifying one of the following three regimes:

(1) S.I.=Streptomycin sulphate 1 g. daily+isoniazid 1,000 mg given in two divided doses with pyridoxine 50 mg. b.d. (After leaving hospital, isoniazid reduced to 600 mg. once daily+pyridoxine 100 mg. once daily.)

(2) S.P.=Streptomycin sulphate 1 g. daily with pantothenic acid 150 mg. daily at the same time+isoniazid 100 mg. b.d.

(3) S.¼=Streptomycin sulphate 0.75 g.+isoniazid 100 mg. b.d.

Each patient received initially sodium *para*-aminosalicylate (P.A.S.) 12 g. daily for six weeks, and after leaving hospital streptomycin and isoniazid were given daily except Sundays.

Subsequent testing of our random selection confirmed that the patients were matched in terms of age, weight on admission, E.S.R., and extent of disease. Positive pretreatment cultures for *Mycobacterium tuberculosis* were obtained in 97 patients. The allocation of the sputum-positive patients showed a slight bias in favour of the S.¼ group—namely, S.I., 32; S.P., 37; S.¼, 28.

RESULTS

The clinical improvement of all patients has been satisfactory. The rate of sputum conversion after one month's and three months' treatment is similar in all three groups, and by six months all patients were culture-negative and have remained so. To date, 56 patients have completed 18 months' chemotherapy. A preliminary analysis of the radiological results on the first 88 patients who had completed nine months' treatment shows similar degrees of improvement. This was based on independent dual reading of films where the identity of the treatment was unknown to the reader.

Thus the accepted criteria of response to treatment of active pulmonary tuberculosis have *so far* shown no evidence that a daily dose of 0.75 g. of streptomycin is inadequate. This trial is still in progress, and the final results will be submitted later.

When patients complained of persistent dizziness or unsteadiness of gait, treatment with streptomycin was stopped. Objective ataxia was observed in most of these patients, but the Romberg test, presence of nystagmus, and caloric tests were only of limited value.

Incidence of Vertigo

	S.I.	S.P.	S.¼	Total
No. of patients	44	46	45	135
,, developing vertigo ..	14	12	2	28 (21%)

Vertigo of a degree to require cessation of streptomycin developed in 28 (21%) patients (see Table). The incidence of vertigo in the S.I. group was 32%, while that in the S.¼ was 4%. The observed difference (28%) is 3.7 times the standard error. Pantothenic acid is in our experience of no value in preventing or diminishing the development of vestibular damage due to streptomycin. Reduction of the daily dose of streptomycin to 0.75 g. has nearly abolished this serious complication.

We are indebted to Dr. Peter T. Main and to Boots Pure Drug Company, who have generously supplied all the 0.75-g. streptomycin viules used in this trial.

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REFERENCE
Stradling, P., and Poole, G. (1958). *Lancet*, **2**, 1066.

"The work of the Nuffield Institute of Comparative Medicine, Zoological Society of London, will be a development of one of the society's traditional activities. For 130 years it has been providing material to medical research workers for the study of isolated problems in comparative anatomy, pathology, haematology, and parasitology. In the past, however, the laboratory facilities were never sufficient to permit exhaustive studies to be made, and the society was not able to employ a research staff of its own to take advantage of the ever-present opportunities for studies in comparative medicine. The variety of material that is available is remarkable. Recently, for example, there was a case of cardio-renal failure in a Malay wild dog; one of coronary thrombosis in an Indian wild ass; and one of cardiovascular degeneration in a hornbill. But once these diagnoses had been made in the post-mortem room by microscopic study of tissues, there was little opportunity of doing further work. . . . In the society's zoological gardens the research workers will have at their disposal pathological material from vertebrates living on almost every conceivable diet. There can be systematic investigation of specific conditions in the living animal, and eventually it will be possible to compare the findings with those of the post-mortem examination." (*Nuffield Foundation Fifteenth Report*, 1960.)

Medical Memoranda

Spondylitis Ankylopoietica in a Uganda African

Spondylitis ankylopoietica (Marie–Strümpell–Bechterew disease) appears to be very rare among the Bantu Africans. A search of the English literature failed to reveal a single reported case in an indigenous African, and there is no record of one in the clinical records of Mulago Hospital during the past eight years—other than that described below. M. Weinbren (1959, personal communication) reports a similar very low incidence in the African population of Johannesburg. Cockshott (1959, personal communication) has, however, occasionally seen it in West Africans at Ibadan. The incidence in American negroes also appears to be low, for Baker *et al.* (1950) had only three cases in a consecutive series of 100 patients with this condition admitted to Duke Hospital in North Carolina. He does not state if these were of pure negro strain.

CASE REPORT

In January, 1959, a male Muganda of about 30 fell off a bicycle he was riding, and five weeks later attended hospital complaining of marked stiffness of the neck after the accident. Though *x*-ray examination of his cervical spine showed no fracture, considerable ossification of his anterior and posterior longitudinal ligaments was noted (Fig. 1). He was subsequently admitted to hospital for investigation.

On further questioning he admitted to some stiffness of the neck for the last 14 years, but stated that it had been much worse since the accident. Apart from some similar stiffness in the rest of his back he had no other complaints. He denied any history of urethral discharge, tonsillitis, dysentery, fevers, or venereal disease. His father was dead, but the patient stated that his father had suffered from a "bad back" and that one of his brothers was similarly affected. His mother, two other brothers, a sister, and his wife and a newly born child were all stated to be well, but it has not been possible to get any of them to hospital for examination. He works as a peasant cultivator, and has lived all his life within 30 miles (48 km.) of Kampala.

FIG. 1.—Cervical spine showing ossification in anterior and posterior longitudinal ligaments, normal disks, and fusion of the zygo-apophysial joints.

Physical examination showed a well-nourished muscular man standing in a posture of fixed flexion of the entire spine. The joints of all four limbs and the temporo-mandibular and atlanto-occipital joints showed a full range of painless movement, but the spine was rigidly immobile in a uniform flexed curve and the costo-vertebral joints were also fixed. There was no mottling of the teeth. The heart, lungs, and abdomen showed no abnormality except that respiratory movement was entirely abdominal owing to fixation of the ribs. There was no urethral discharge. The blood-pressure was 130/80. No sugar or albumin was present in the urine.

The Kahn test was negative and agglutination reactions for typhoid and brucellosis were also negative. Serum alkaline phosphatase was 6 units/100 ml. The E.S.R. was 7 mm./hour (Wintrobe). Radiological examination showed partial ossification of the anterior and posterior longitudinal ligaments and both lateral ligaments throughout the spine, with bony bridging between most of the vertebral bodies. The zygo-apophysial joints were completely fused from the second cervical to the first sacral on both sides. The dorsal and lumbar vertebral bodies showed "squaring" of their contours in lateral projection with slight osteoporosis in the lumbar region. The vertebral borders and surfaces were not eroded and the intervertebral disks were normal. There was some ossification of the interspinous ligaments in the lumbar region, and the costo-transverse joints were fused. The sacro-iliac joints showed irregular erosions with surrounding sclerosis, and the joint spaces were widened (Fig. 2). The bones of the wrists, hands, ankles, and feet were normal. Unfortunately the patient refused further examination.

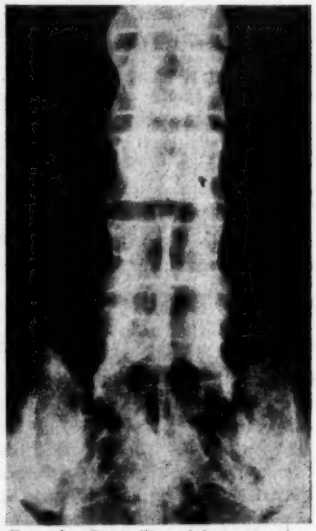

FIG. 2.—Sacro-iliac joints showing erosions; lower lumbar spine showing ligamentous ossification; normal disks with fusion of zygo-apophysial joints.

COMMENT

The apparent rarity of spondylitis ankylopoietica among Africans requires careful consideration of other possible diagnoses in this case. Reiter's syndrome (which is not uncommon in Uganda) and rheumatoid arthritis were rejected as possible alternatives owing to the distribution and nature of the *x*-ray changes demonstrated and the absence of any clinical suggestion of these diseases.

The common spondylitis of Africans is inflammatory, and, though ossification of ligaments occurs with it, its common characteristics are destruction of vertebral bodies and intervening disks, neither of which were found in the present case.

Our thanks are due to the Director of Medical Services, Uganda, for permission to publish this case.

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REFERENCE

Baker, L. D., Coonrad, R. W., Reeves, R. J., and Hoyt, W. A., jun. (1950). *J. Bone Jt Surg.*, 32A, 848.

Reprints of an article by the Joint Tuberculosis Council printed in *Tubercle*, October, 1960, "Tuberculosis: Report on the Reception of Ex-patients in Respect of Re-employment and Superannuation, Life Assurance and Emigration," are now available (price 1s.) from Dr. R. L. Midgley, Hawkmoor Chest Hospital, Bovey Tracey, Devon.

Reviews

SOCRATES ON THE HEALTH SERVICE

Socrates on the Health Service. Dialogues of To-day. From the *Lancet*. (Pp. 102. 5s.) Bedford: The Sidney Press Limited. 1960.

Socrates was executed for subverting the youth of Athens from the principles of democracy at a time when Athens had been shaken by the disastrous end of the Peloponnesian war. It is less dangerous nowadays to question the conventional wisdom, and a large number of readers of the *Lancet* must have enjoyed the dialogues on the Health Service in Socratic form which have now been published as a paperback. An introductory quotation from David Hume points out that the dialogue form is of special value in circumstances where the material is so familiar as to require dramatization to refresh it, or again where differences are so unresolvable that there is no alternative to an actual display of the various opinions. The whole thing is wittily done, with characters such as the Marxist *Erythro* and the Freudian *Analyticus*, and we are entranced by the gentle satire on the foibles of our colleagues. Not infrequently, too, we feel that jangling of the synapses which records the reception of an unfamiliar or painful idea.

A great variety of topics is covered, from age and leadership to appearances on television, from euthanasia to the merits of pure and applied science. The book can be compared with Parkinson's Law or Cornford's *Microcosmographia Academica* in that there is much in it that is likely to be permanently assimilated into the corpus of medical thought. An example is the account of the grammar of medicine, in which the positive is "specially interested," the comparative is "specialist," and the superlative is "head of a special department." Very apt, too, is the remark that the whole-timers have become a kind of medical clergy. If the book conveys one particular lesson it is that men and professions are governed by themselves, and if men find that desirable things cannot be done or that they are tied down like Gulliver in a mesh of red tape the fault is usually their own. But then, I am on the side of Socrates in the dialogue on Colleges Galore.

Socrates, who was known as "the wisest of men," was clearly also one of the most irritating, and like George Bernard Shaw and Gandhi he does not always play fair. Indeed, the trouble with this book is that one so often wants to answer back. To give but one example, how easy life would be if, as Socrates suggests, there is usually but one wise course of action and not many, when a decision has to be made about a course of action. How gleefully, too, one can imagine Sir Francis Walshe tearing to ribbons the dialogue on Professions Supplementary. And having sat under such excellent chairmen of medical committees as Lord Balfour, Lord Lindsay, and Sir William Goodenough, I do not find anything paradoxical in a non-medical head of the Health Service. The trouble with disputation and getting back to first principles is that the conclusions are so often contradicted by the results of experience. Nevertheless, this is no excuse for not thinking, for much of our life's work is not susceptible to guidance by experiment, and these provocative discussions will do good in stimulating the reader to think just where he is and where he imagines he is going.

L. J. WITTS.

CLINICAL PHYSIOLOGY

Clinical Physiology. Edited by E. J. Moran Campbell, B.Sc., Ph.D., M.D., M.R.C.P., and C. J. Dickinson, B.A., B.Sc., B.M., M.R.C.P. Foreword by Sir Robert Platt, Bt., M.D., M.Sc., LL.D., F.R.C.P. (Pp. 530+xi; illustrated. 50s.) Oxford: Blackwell Scientific Publications. 1960.

This is an interesting and important book, for it is an unsuccessful attempt to write on a fundamental subject. The reasons for the lack of success are given by the authors in the preface, and include the observation that "applied physiology and functional pathology have, as yet, little place in teaching." Yet this is despite the well-known textbook, *Applied Physiology*, which comes from the same School of Medicine and has been written over many years. Further, the authors, with students and postgraduates in mind, have deliberately not endeavoured to cover the whole subject but to discuss those aspects that can be profitably presented from a clinical standpoint rather than from that of academic physiology. The third outstanding reason is their reluctant decision to exclude neurology, not even including a mere chapter.

The result is that while this is a useful textbook for a membership student on present observations and advances in clinical laboratory medicine, it almost completely ignores any pointers for new work from the academic laboratories or the applications of experimental embryology, zoology, physiology, biophysics in relation, for example, to genetics, congenital diseases, disorders of the nucleus, and membrane permeability. Where the nervous system is concerned, admittedly the least studied by the experimental physician, the mass of modern work arising out of ionic movements across cell membranes, synaptic conductors, biophysics, and electron microscopy is excluded.

The book is a useful guide to the newer clinical techniques but disappointing to one who wants to know what new ideas are coming back to the basic (or is it "fundamental"?) sciences from the clinical scientist. But within these limitations it is excellently written and presented. The authors are to be congratulated on their orderly presentation of each chapter in four sections—normal and disordered function, underlying principles of new tests, and applications in modern practice.

A. ST. G. HUGGETT.

DERMATOLOGY WITHOUT FRILLS

Manual of Skin Diseases. By Gordon C. Sauer, M.D. (Pp. 269+xvii; illustrated. 70s.) London: Pitman Medical Publishing Co., Ltd. 1960.

Dr. Sauer, who works in Kansas, has produced a book that has considerable merit. It is written for the general practitioner who has knowledge of general medicine and has contact with dermatological patients but limited knowledge of the subject. The book is almost a synopsis of dermatology and includes the bare minimum. I am impressed that the bare minimum is generally adequate for the purpose it is intended to serve. The work is entirely practical, without frills, and is arranged and presented with this practical objective in view.

The clinical descriptions are limited to essentials and are effectively presented. Remarks on aetiology and prognosis are blunt and valuable; treatment is generally good and restricted to a few practical measures which would be accepted as sound by most dermatologists. Views expressed are up to date and carry a ring of experience and authority. Dr. Sauer is evidently a man with plenty of common sense and an understanding of human nature. Not all his practice conforms to the

British pattern, as would be expected, but it is none the worse for this. Occasionally American drugs are prescribed which are not normally available here. With very few exceptions the pattern of presentation is acceptable to the British reader, especially to the busy practitioner. Very rarely indeed is an American word used that would jar, such as "the psychoitchical" patient. The chapter on history-taking is written in conversational form but it does make some important and useful points. The occasional heavy-typed emphasis on essential features is a good American habit—"Syphilis Pearls," "Do's and Don'ts," etc. Some features are introduced which are unusual and valuable and promote thought. Suggestions regarding the follow-up treatment of patients after their first visit are good. The indication that particular affections are found in certain geographical areas is important, though the information given only refers to the U.S.A. The chapter on local treatment is good; but that on vascular diseases is not so well presented. The sections on lichen planus and on bacteriology, and those on animal parasites and exfoliative dermatitis respectively are barely adequate. The final chapter with its "Dictionary Index" is excellent and should prove most valuable to the practitioner.

The illustrations are lavish and very good, and include 28 excellent colour plates culled in the main from the libraries of pharmaceutical firms. The format is attractive and the size, weight, and price of the work are most acceptable. It is not primarily a book for the undergraduate student or for the specialist, but is to be recommended for the library of the general practitioner.

J. T. INGRAM.

TUBERCULOUS MENINGITIS

La Méningite Tuberculeuse et son Traitement. By Jean Fouquet. (Pp. 236; illustrated. N.F. 30.) Paris: G. Doin et Cie. 1960.

Dr. Fouquet has had considerable experience in the treatment of tuberculous meningitis and has published well over 20 papers on this subject in the last 12 years. In this book he summarizes his experience by ranging over the whole field from aetiology and pathology, the clinical picture, diagnosis and differential diagnosis, to treatment and sequelae.

This he does in a unique fashion—the book is neither a monograph in which the relevant world literature is critically discussed and analysed, nor is it a detailed objective analysis of his own material. He deals with the well-known features of the disease and its treatment in a light but didactic and imperious way, often emphasizing his points by illustrative case histories rather than by more weighty proof. His main interest is treatment, but he spends too much time on describing obsolete methods. Among the controversial issues in this field, he has now abandoned intrathecal treatment in the average case, though he will use it in complicated cases. He only occasionally uses steroids as adjuvants, although he recognizes that they can produce striking amelioration of symptoms, at least for a short time.

The book is well printed. Its style is light, easy and clear. Unfortunately, the 33 illustrations are printed on poor paper and are therefore of no value. The main disadvantage of the book, however, is that it is far from clear for whom it is intended: for the student there is far too much on one disease; to the research worker and the expert it contributes nothing. The book is a description of a superficial impression of a large body of material which has not been adequately digested or analysed and has hence been wasted.

JOHN LORBER.

SURGICAL TEXTBOOKS

Cole and Elman Textbook of Surgery. By Warren H. Cole, M.D., with 49 contributing authors and consultants. Foreword by Evarts A. Graham. Seventh edition. (Pp. 1,224+xxi; illustrated. £7 7s.) London: Staples Press.

Christopher's Textbook of Surgery. Edited by Loyal Davis, M.D. Seventh edition. (Pp. 1,551+xix; illustrated. £5 19s.) Philadelphia and London: W. B. Saunders Company. 1960.

Both these well-known American textbooks of surgery are so well established that they need not fear criticism from an English reviewer. Each book, now in its seventh edition, has undergone extensive revision. Both books enjoy considerable popularity outside the United States, though Christopher is probably the better known in Britain. Apart from their country of origin their other points of similarity include double-column layout, good indexing, a fairly full bibliography to each chapter, and multiple authorship—Christopher has 82 and Cole and Elman 50 contributors.

There are some interesting differences between these two works. Christopher, the larger and less expensive book, devotes much less space to such general subjects as shock, wound healing, and infection. But, if Christopher can be faulted for saying too little on these subjects, then Cole and Elman may perhaps be criticized for saying too much. Excluding the basic chapters, Christopher contains roughly twice as much as Cole and Elman on the regional and systemic diseases. Multiple authorship leads to some anomalies: thus Cole and Elman includes a very adequate chapter on the thyroid while Christopher is somewhat thin on this subject; by contrast the chapter on hernia in Christopher seems unusually detailed. Despite some inevitable lack of balance between the different parts the many contributors do provide a pleasing variety of style. Notable among the outstanding parts of each book are the excellent chapters on cardiac and vascular surgery.

Both books are well produced, but some of the illustrations in Cole and Elman are of poor quality. Cole and Elman, notwithstanding its higher price, seems more suitable for the undergraduate, while Christopher seems better for the postgraduate reader.

R. S. MURLEY.

CIBA MEDICAL ILLUSTRATIONS

Ciba Collection of Medical Illustrations. Volume I: *Nervous System.* (Pp. 167; illustrated. 50s.) Combined with *Supplement on the Hypothalamus.* (Pp. 24.) 1953. Volume II: *Reproductive System.* (Pp. 304; illustrated. 92s. 6d.) 1954. Volume III: *The Digestive System.* Part I: *Upper Digestive Tract.* (Pp. 206; illustrated. 90s.) 1959. Part III: *Liver, Biliary Tract, and Pancreas.* (Pp. 165; illustrated. 75s.) 1957. Illustrated by Frank H. Netter, M.D. Edited by E. Openheimer, M.D. New Jersey: Ciba Pharmaceutical Products, Inc.

For several years Ciba have distributed to members of the medical profession loose-leaf portfolios containing colour illustrations of normal and pathological anatomy from the brush of Dr. Frank Netter. The success of this venture led eventually in 1953 to the commissioning of a series of volumes, each devoted to a separate system, portrayed by this artist, which were to be offered to the medical profession as a non-profit service

to be sold at the basic cost of publication and distribution. Up to 1959 four such volumes had been produced: these are Vol. 1, Nervous System, 1953 (fourth printing 1958); Vol. 2, Reproductive System, 1954; Vol. 3, Part III, Digestive System, Liver, Biliary Tract, and Pancreas, 1957; Vol. 3, Part I, Digestive System, Upper Digestive Tract, 1959.

Vol. 1 contains 122 plates, with an added supplement on the hypothalamus illustrating some modern views on the neuro-secretions of the supra-optic and para-ventricular nuclei. Some of the plates are in schematic form, and it is clear that a lot of thought has been given to these diagrams in order to concentrate as much information as possible in each one. The majority, however, are devoted to the anatomy of the system and to certain of the commoner pathological conditions, together with, in some instances when helpful, an illustration of a patient suffering from the condition. As an example, under "birth injuries" we have an illustration of a brain showing a pial haemorrhage over the upper motor cortex and by its side a picture of a child with a spastic diplegia. These remarks apply to the arrangement adopted throughout all the volumes. As the title "The Ciba Collection of Medical Illustrations" indicates, the volumes are essentially atlases, but there is an explanatory text accompanying each plate in which a concise description of the condition—or of the anatomy and physiology when appropriate—is given. These commentaries have been written by eminent and well-known specialists in their particular branches; for instance, the text of the section on the autonomic system has been written by Dr. Albert Kuntz, and similarly with all the other sections throughout the work.

Vol. 2 contains no fewer than 233 plates illustrative of the reproductive system of both sexes, including sections on pregnancy and its diseases, the mammary gland, and the intersexes. As many of the plates contain five or six separate pictures it will be appreciated what a large amount of labour went into the production.

Vol. 3 on the Digestive System deals with so large a subject that it has been found necessary to publish it in three books, of which Parts I and III dealing respectively with the "Upper Digestive Tract" and "Liver, Biliary Tract, and Pancreas" are available for review. They contain between them 305 plates. In these sections there there is a greater number of plates devoted to the demonstration of diagnostic procedures and of physiology. At the end of each volume there is a comprehensive index and to some parts an extensive list of references.

Frank H. Netter is not only a most skilled artist but has the advantage of being medically qualified and therefore able to appreciate the significance of the various points he is depicting. This is particularly valuable in the schematic diagrams illustrating anatomical and physiological features and diagnostic methods. For the most part the paintings appear to be in water-colour, which lends itself well to these subjects, but recently the artist says he has used gouache, poster colours, and pastels. In some instances the colouring may appear at first sight to be rather too flamboyant, but this is excusable especially in conventionalized schematic drawings, where certain features require emphasis. The hypercritical reader may wonder at the choice of subjects for the plates, but in all probability from the thousands of possibilities those had to be chosen which were available at the time to the artist and his collaborators. On the whole we consider the choice has been not only good but comprehensive. The compilers indeed warn in the preface, "Completeness is not our aim. The drawings are intended to supplement rather than to replace the standard works." A word of praise must be given to the printers and the colour engravers for the excellence of their work. In no plate in the volumes under review has there been any disorientation of the colour blocks. This indicates perfection of reproduction, and the general format of the books is of a correspondingly high standard.

From the days of Leonardo and Vesalius anatomical and pathological illustration has played an important part in the spread of knowledge. There are those for whom the written word is more important and memorable, but the modern tendency is certainly in favour of the economy both of space and time which the illustration provides, especially so for the visualist. It is, of course, impossible to do justice to such a monumental work as this in a short review, but there can be no doubt that these colourful illustrations will be welcome in any medical centre and particularly in those engaged in teaching. We shall therefore look forward to the further volumes with pleasant anticipation.

NORMAN C. LAKE.

TREATMENT OF EYE INFECTIONS

Antibiotics and Sulphonamides in Ophthalmology. By Arnold Sorsby and Joseph Ungar. (Pp. 117+ix; illustrated. 12s. 6d.) London, New York, Toronto: Oxford University Press. 1960.

This small booklet is a useful summary of our present knowledge of the value of antibiotics and the sulphonamides in the treatment of infective conditions of the eye. There is no doubt that since the introduction of these drugs the prognosis of most external ocular infections, with the marked exception of those caused by the smaller viruses, has been revolutionized, and that in communities which have an adequate medical service at their disposal many such conditions—for example, infective corneal ulcers or ophthalmia neonatorum—have ceased to be major causes of gross visual disability. In Great Britain both Sorsby and Ungar have been pioneers in the field of adapting the various chemotherapeutic agents to ophthalmic practice, and this summary of their work, incorporating fully the researches of others in the same field over the last two decades, is an eminently useful clinical guide, giving details of the methods of systemic and local application of these drugs, the concentrations attained in the ocular tissues, and their clinical indications and contraindications. An authoritative and clinically sound survey of these important problems is a welcome addition to ophthalmic literature.

STEWART DUKE-ELDER.

RADIOTHERAPY OF CANCER

Cancer. Edited by Ronald W. Raven, O.B.E.(Mil.), T.D., F.R.C.S. Volume 5. Part IX. *Radiotherapy.* (Pp. 406+19+viii; illustrated. 85s.) London: Butterworth and Co. (Publishers) Ltd. 1959.

This part of volume 5 of the work *Cancer* covers the contribution of radiotherapy in the treatment of cancer. The early chapters are concerned with the physical aspects of the ionizing radiations in current use, the subject matter being presented in such a manner

as to be readily understood by readers not specializing in radiotherapy. An excellent, concise contribution on the biological basis of radiotherapy by Professor P. C. Koller should give all radiotherapists food for thought, and the list of references indicates the number of workers now contributing to the field of radiobiology. The chapter, however, exposes gaps yet to be filled in our knowledge of the factors influencing effects of ionizing radiations on tumour and tumour bed, without which, one feels, further progress in radiotherapy will not be achieved.

The remaining contributions are concerned with the clinical applications of radiotherapy in current use, and, though they do not reveal anything fundamentally new, they are comprehensive. Special mention must be made of the chapters on malignant tumours of the maxillary antrum and ethmoids and the pharynx. These difficult sites for radiotherapeutic treatment are very well discussed, the text being supported by excellent illustrations. The same also applies to the section on carcinoma of cervix and corpus uteri. Gynaecologists and radiotherapists alike will find this well-illustrated contribution, which presents the various techniques in use to-day, a guide and help in determining treatment policy. There are also useful chapters on radioisotopes and radiation protection. The contribution on carcinoma of the breast could be expanded with benefit. More detailed information on other radiotherapeutic techniques, preferably by illustration, would be appreciated. In conclusion, this book presents concisely the contemporary British approach to the clinical practice of radiotherapy and can be recommended also to students of the specialty.

N. A. SHARPLES.

TOXIC ALIPHATIC FLUORINE COMPOUNDS

Toxic Aliphatic Fluorine Compounds. By F. L. M. Pattison, M.A., Ph.D., F.R.I.C., F.C.I.C. Foreword by Sir Rudolph A. Peters, M.D., F.R.S. (Pp. 227+xi; illustrated. 18s.) Amsterdam, London, New York, Princeton: Elsevier Publishing Co. 1959.

Although the toxic aliphatic fluorine compounds referred to in this monograph are of little or no industrial importance, they are of great interest to the biologist. The classical work of Sir Rudolph Peters on fluoroacetate illustrated how a toxic compound could be used to throw light on normal metabolic processes.

The author is a chemist who has contributed a great deal to the preparation of these compounds. Many readers will be surprised to see from the tables that data on over 350 compounds are available. The information on toxicity is, however, very meagre and limited for the most part to the LD_{50} for single doses to mice. Hitherto even this scrap of information was buried in the chemical rather than the biological literature. The author has no personal contribution to make to the discussion of the nature of the toxic effects of these compounds, and he extrapolates freely from the work of others. Indeed, it is only by constant repetition that he is able to expand the matter to the dimensions of a monograph.

The opening sentence to the effect that criminologists are continually on the alert for poisons capable of committing "the perfect murder" is more in keeping with a "whodunit" than with reality. However, the book is otherwise mainly factual, and it should be a useful reference book to one group of organo-fluorine compounds.

J. M. BARNES.

BOOKS RECEIVED

Review is not precluded by notice here of books recently received.

The Ethics of Medical Practice. By John Marshall, M.D., F.R.C.P.(Ed.), M.R.C.P.(Lond.), D.P.M. (Pp. 164. 21s.) London, Darton, Longman and Todd. 1960.

Aids to Forensic Medicine and Toxicology. By Sir W. Bentley Purchase, C.B.E., M.C., M.B., M.A., M.R.C.S., L.R.C.P. Thirteenth edition. (Pp. 260+viii. 12s. 6d.) London: Baillière, Tindall and Cox. 1960.

Memories of a Doctor in War and Peace. By Isabel Hutton, C.B.E., M.D. (Pp. 348. 25s.) London, Melbourne, Toronto: Heinemann. 1960.

Good English for Medical Writers. By Ffrangcon Roberts, M.A., M.D., F.F.R. (Pp. 179+ix. 17s. 6d.) London: William Heinemann Ltd. 1960.

A Study of Home Accidents in Aberdeen. An Investigation Financed by the Nuffield Provincial Hospitals Trust. By Ian A. G. Macqueen, M.A., M.D., D.P.H., F.R.S.H. (Pp. 99+viii. 12s. 6d.) Edinburgh and London: E. and S. Livingstone Ltd. 1960.

Essentials of Medicine for Dental Students. By A. C. Kennedy, M.D., M.R.C.P.E., F.R.F.P.S. Foreword by L. J. Davis, M.D., F.R.C.P.Lond. and Edin., F.R.F.P.S. (Pp. 272+viii; illustrated. 25s.) Edinburgh and London: E. and S. Livingstone Ltd. 1960.

Artefacts and Handling and Processing Faults on X-ray Films. By E. A. Zimmer. (Pp. 67; illustrated. $5.75.) New York and London: Grune and Stratton. 1960.

The Boys' Book of Medical Science. By L. R. Celestin. (Pp. 143; illustrated. 10s. 6d.) London: Burke Publishing Company Ltd. 1960.

Famous Criminal Cases VI. By Rupert Furneaux. (Pp. 256. 21s.) London: Odhams Press Ltd. 1960.

The Management of Fractures and Soft Tissue Injuries. By the Committee on Trauma, American College of Surgeons. Based on *An Outline of the Treatment of Fractures* seventh edition and *Early Care of Acute Soft Tissue Injuries* second edition. (Pp. 372+xix; illustrated. 35s.) Philadelphia and London: W. B. Saunders Company. 1960.

Eye Signs in General Disease. By F. Herbert Haessler, M.D. (Pp. 118+xv. 46s.) Springfield, Illinois: Charles C. Thomas. 1960.

The Case Reports and Autopsy Records of Ambroise Paré. Compiled and edited by Wallace Hamby, M.D., F.A.C.S. Translated from J. P. Malgaigne's *"Œuvres Complètes d'Ambroise Paré,"* Paris, 1840. (Pp. 214+xx. 52s.) Springfield, Illinois: Charles C. Thomas. 1960.

Supplement to Catalogue of Lewis's Library 1957-1959, including a classified index of subjects with the names of those authors who have treated upon them. (Pp. 306. 10s. 6d.) London: H. K. Lewis and Co., Ltd. 1960.

Emotional Maturity. The Development and Dynamics of Personality. By Leon J. Saul, M.A., M.D. Second edition. (Pp. 393+xxi. 52s.) Philadelphia and Montreal: J. B. Lippincott Company. 1960.

Attenuated Infection. The Germ Theory in Contemporary Perspective. By Harold J. Simon, M.D., Ph.D. Forewords by Rene J. Dubos, Ph.D., and Walsh McDermott, M.D. (Pp. 349+xvi; illustrated. 80s.) Philadelphia and Montreal: J. B. Lippincott Company. 1960.

Semeiotica Strumentale delle Vie Biliari. By A. Infranzi, G. Esposito, and S. di Gaeta. (Pp. 517+xv. No price.) Turin: Minerva Medica. 1960.

Handbook of Abnormal Psychology. An Experimental Approach. Edited by H. J. Eysenck, Ph.D. (Pp. 816+xvi; illustrated. £6.) London: Pitman Medical Publishing Company Ltd. 1960.

Ciba Foundation Symposium on Haemopoiesis. Cell Production and Its Regulation. Editors for the Ciba Foundation: G. E. W. Wolstenholme, O.B.E., M.A., M.B., M.R.C.P., and Maeve O'Connor, B.A. (Pp. 490+xii; illustrated. 60s.) London: J. and A. Churchill Ltd. 1960.

Nose and Throat Histology: Photomicrographs. By James A. Moore, M.D. (Pp. 64+vii; illustrated. 52s. 6d.) New York and London: The Macmillan Company. 1960.

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THE RIDDLE OF INFECTIOUS MONONUCLEOSIS

The clinical features of "glandular fever" were described by Pfeiffer in 1889, but a long period of confusion about its differentiation followed. The work of T. P. Sprunt and F. A. Evans[1] in the United States and of H. L. Tidy and E. B. Morley[2] in Great Britain led to its general recognition as a distinct clinical entity. During the last 20 years, however, the accumulated clinical, epidemiological, and laboratory data have again added complexities to the picture, chiefly perhaps because of the failure to identify an aetiological agent. In modern usage the disease is now known as infectious mononucleosis, but in a recent important field study F. G. Hobson and his colleagues[3] still avoided this term as "possibly misleading." The overall incidence appears to be increasing. In an analysis of 1,779 cases admitted to hospital in Stockholm during the period 1940–57 J. Ström[4] showed that there had been a sixfold rise in the number of cases and a 4.4-fold rise in relation to the population. Though better diagnosis might have had some influence, this was negligible during the last 15 years, during which an unbroken rise had occurred.

Though the disease is of low infectivity and to most clinicians presents sporadically, many outbreaks have been reported, especially in colleges and institutions, and a virus is generally assumed to be the cause of it. But all attempts to cultivate a virus from patients, either in chick embryos[5] or in tissue cultures of many forms,[6] have failed, and, though in one out of five attempts the disease is said to have been transmitted to a volunteer,[7] all transmission experiments in the laboratory have been uniformly unsuccessful. The postulated virus, perhaps like that of the common cold, must require highly specialized conditions for its growth *in vitro*.

[1] Sprunt, T. P., and Evans, F. A., *Bull. Johns Hopk. Hosp.*, 1920, **31**, 410.
[2] Tidy, H. L., and Morley, E. B., *Brit. med. J.*, 1921, **1**, 452.
[3] Hobson, F. G., Lawson, B., and Wigfield, M., ibid., 1958, **1**, 845.
[4] Ström, J., *Acta med. Scand.*, 1960, **168**, 35.
[5] Bang, J., ibid., 1943, **113**, 304.
[6] Evans, A. S., *Amer. J. Hyg.*, 1960, **71**, 342.
[7] Wising, P. J., *Acta med. Scand.*, 1939, **98**, 328.
[8] Reimann, H. A., *Arch. intern. Med.*, 1960, **105**, 779.

H. A. Reimann[8] has recently introduced the idea of a "spectrum bar" for each infectious disease to denote the proportions of the various grades of severity, from inapparent infection to fatal cases, met with at any given time and place. As in many infections, the spectrum of infectious mononucleosis contains a high proportion of mild or even abortive cases. These have usually a short (4–18 days) incubation period and may appear in outbreaks; a high proportion of the cases are children, while males in all age groups preponderate. Patients may present with mild fever, slightly enlarged posterior cervical or other glands, and perhaps slight sore throat, but can hardly be diagnosed without a white blood count, which shows lymphocytosis and the presence of the characteristic abnormal lymphocytes or monocytes. The Paul–Bunnell (P.B.) test for heterophile antibody in the blood serum is frequently negative. There are other P.B.-negative or low-titre cases, which may not be so mild and may have a rash, generally of rubelliform type but lasting longer (about 5 days). This composite group of P.B.-negative or low-titre cases has been considered by many authors to represent a different disease from that of the well-marked P.B.-positive cases, which usually are more severe, with extensive adenopathy, angina, sometimes with tonsillar exudate as in diphtheria, and some grades of hepatitis. These are usually sporadic cases, in adults, and in the 15–19 age group there is a preponderance of females. If there is a known contact, the incubation period may apparently be as long as 2–3 months. With these clinical and epidemiological distinctions broadly between P.B.-negative and P.B.-positive groups, the idea that infectious mononucleosis is not one but two diseases has gained much acceptance during the last five years.

A recent contribution[6] goes a stage further, and suggests that the disease may exist in three phases: (1) a primary abortive phase characteristic of childhood infections and with an epidemic tendency; (2) an intermediate viraemic phase with a tendency to rashes, and with heterophile antibody not yet detectable or of low titre, and (3) a phase of tissue reaction to virus multiplication in secondary sites, characteristically in young adults, with an apparently long incubation period, perhaps because of missed diagnosis in the earlier stages, and strongly P.B.-positive. Phase 3 may be associated with the severe complications reported increasingly in recent years, such as haemolytic anaemia, thrombocytopenic purpura, and the Guillain–Barré syndrome of symmetrical bilateral polyneuritis. Such complications of an allergic type are now widely suspected of

being examples of auto-immune disease, whereby abnormal antigens—foreign to the body—may be formed from denatured proteins by virus or other action, with resulting production of antibodies in or on particular organs or tissues. The consequent auto-immune reaction at these sites produces the localized damage to the organ or tissue concerned. In the case of infectious mononucleosis it might conceivably be abnormal antibodies that are produced by the abnormal but "immunologically competent" cells of the lymphocyte series. The limited duration of the allergic complications could fit in with such a view. Is infectious mononucleosis then a composite disease with both an infectious stage and a potential or actual auto-immune phase?

TREATMENT OF SQUINT IN CHILDREN

It is seldom appreciated that the treatment of squint is not merely a matter of making the eyes straight. Nor does it follow, if the deviation is overcome either by spectacles correcting the refractive error or by surgical treatment, that each eye will have normal vision and the two eyes will function together in normal binocular association.

In ordinary circumstances binocular vision gradually develops during the first four or five years of life, provided the eyes are straight. But if squint is constant during early childhood, so that only one or other eye can be used for direct vision, not only is the development of binocular function arrested, but the child also gradually loses the function of binocularity if it existed before the onset of the squint. In addition, if the squint is confined to one eye (uniocular squint), there is a gradual loss of the vision of the squinting eye (amblyopia ex anopsia), so that the eye becomes "lazy" or amblyopic owing to the mental process of suppression. If the treatment of the amblyopia is neglected, particularly if the patient is a young infant, the squinting eye may fail to retain the ability to use its fovea as the central point of fixation, and an eccentric retinal point away from the fovea may assume a straight-ahead type of projection. The establishment of such eccentric fixation is usually preceded by the development of anomalous retinal correspondence, which constitutes an attempt on the part of the patient to employ the two eyes together in a low-grade form of "binocular" association. Eccentric fixation is a relatively unrewarding acquisition because the eccentric point of fixation is incapable of a high degree of visual acuity, and the further it is situated from the true fovea the worse the visual acuity.

Consequently the treatment of squint in children may be a matter of some urgency and must be planned along certain well-defined lines. It is, of course, important to restore parallelism of the visual axes by correction of refractive errors, or, if this fails, by accurate and (if necessary) repeated surgical treatment in order to assist the natural development of normal binocular association and to avoid the adverse psychological effect of a squint on both child and parents. It is also important to apply the principles of orthoptic practice to develop and improve binocular vision. But the initial aim of treatment must be to restore and preserve the visual function of the squinting eye as soon as the squint is diagnosed. Unfortunately, however, children suffering from squint are rarely treated early enough, either from delay in diagnosis, largely owing to the fact that the simple "cover test" is not used, or from waiting to see if it will get better. But no true squint ever rights itself, and no child is too young for some sort of treatment.

Recently the importance of diagnosing eccentric fixation, which demands the use of special instruments, has been emphasized by K. C. Wybar and B. Thatcher.[1] They state that occlusion of the non-squinting eye in cases of uniocular squint with eccentric fixation is contraindicated because it serves only to foster the eccentric fixation and to make its eradication more difficult. This may explain some of those cases of squint in which prolonged occlusion of the unaffected eye has failed to produce any tangible improvement in the visual acuity of the affected eye, and to which the terms "congenital amblyopia" or "intractable amblyopia" have previously been given.

When eccentric fixation is not fully stabilized, it may sometimes be possible to restore central fixation merely by occlusion of the affected eye for a few months. But in established cases it is essential to adopt a more active form of treatment. In recent years C. Cüppers[2] has shown that it is often possible to restore normal foveal fixation by a process of concentrated stimulation of the fovea, using after-images and the entoptic appearance of Haidinger's brushes. This treatment is time-consuming, requires expensive equipment, and is practicable only for a co-operative and intelligent patient. It cannot as a rule be applied to children under the age of 6 years, and at present it is largely used in cases that have received no or little previous treatment. Its value in children much over the age of 8 or 9 years is also questionable, for there may be a risk of causing an

[1] Wybar, K. C., and Thatcher, B., *Brit. J. Ophthal.*, 1960, 44, 472.
[2] Cüppers, C., *Klin. Mbl. Augenheilk.*, 1956, 129, 579.
[3] Chavasse, F. B., *Worth's Squint*, 1939, 7th ed. London.

annoying diplopia if normal binocularity fails to be established. Moreover, at an age when education is becoming increasingly important, prolonged and concentrated treatment may be inadvisable, since it necessitates daily (or at least tri-weekly) attendance with several hours at each session.

This treatment, to which the term "pleoptics" has been given, has already proved to be of value in selected patients, especially in those tragic cases, sometimes met with in adult life, in which serious disease or injury has overtaken the previously normal-sighted eye of a person whose other eye has been highly amblyopic since childhood owing to a neglected squint. Even when eccentric fixation has been present for many years, once central fixation has been established rapid improvement of vision ensues. Indeed, it has been known for a patient, previously signed up as blind, to qualify for removal of his name from the Blind Register.

Early diagnosis and treatment of squint are too often neglected. In view of the hereditary factor in the aetiology of squint, there is much truth in what F. B. Chavasse[3] wrote on its early diagnosis and treatment: "The ophthalmological examination of *every* newborn child and the estimation of the refraction of *every* infant, say, at the age of twelve months, are reasonable counsels, but, in the present state of medical and public opinion, they are counsels of perfection only. On the other hand, the medical profession should, and can, advise the *ophthalmological care of apparently normal infants born of squinting stock*, as well as the care of the apparently normal younger brothers and sisters of a child who has manifested a squint."

"CELBENIN"-RESISTANT STAPHYLOCOCCI

The history of the antibiotic treatment of staphylococcal infections is a tribute to the ability of *Staph. aureus* to develop resistant strains to one drug after another. Originally all but a few strains were sensitive to penicillin, but this happy state did not last long, and within a few years penicillinase-producing, and therefore penicillin-resistant, staphylococci were becoming too familiar inhabitants of hospital wards. The tetracyclines provided a temporary respite, but after an initial delay resistant strains appeared in hospital. As at this stage it seemed possible that the majority of hospital staphylococcal infections might ultimately be caused by untreatable staphylococci, erythromycin was made the subject of well-observed restrictions in many parts of the world. By confining its use to the most serious infections the level of resistant strains was kept low, and until recently erythromycin has been for many the first choice for seriously ill patients whose condition warranted treatment before the results of sensitivity tests could be known.

In the last few years the position has improved, and novobiocin, oleandomycin, vancomycin, and ristocetin have become available. But either because resistance was a problem, or for lack of bactericidal action, or because of toxicity or inconvenience of administration, a better antistaphylococcal antibiotic was required. It was provided in the shape of dimethoxyphenecillin, or "celbenin," the trade name of one of the first-fruits of the isolation in the Beecham Research Laboratories of the penicillin nucleus, 6-amino-penicillanic acid.[1] Celbenin is not perfect. It is much less active than penicillin G against staphylococci, and substantial levels have therefore to be maintained in the blood. As it is absorbed and excreted rapidly, the frequent injection of large doses is necessary. But if one good compound can be made it is reasonable to hope that other better ones will follow, and that it will be possible to find one that can be given by mouth. The great advantage of celbenin is that it is not destroyed by penicillinase, and that up to now no strains of naturally occurring *Staph. aureus* had been found to be resistant to it. This is no longer the case, as three letters in our correspondence columns show.[2–4]

Dr. Patricia Jevons has examined 5,440 strains at the Staphylococcus Reference Laboratory, and from one hospital has found a small group of strains from three people which were inhibited by 6–25 μg./ml. of celbenin instead of the usual 2–5 μg./ml. The strains were all of one phage type belonging to Group III, and were isolated from septic lesions as well as from one patient's nose. It was clear that they could not have come from the one patient treated in the hospital with celbenin.

At first sight the estimate that celbenin-resistant strains constitute less than one in 5,000 of the total staphylococci in hospital is reassuring. But if it is looked at more carefully at least two reservations should be made. From the first it has been known that resistant strains of *Staph. aureus* could be produced artificially by contact with celbenin. Resistance is not apparently due to destruction of celbenin. The resistant strains appear relatively normal, and, so far as is known, are virulent. If this can be done in the laboratory, it is not inconceivable that it will happen in the ward. The second reservation is that the position now has an uncomfortable resemblance to

[1] *Brit. med. J.*, 1960, 2, 720.
[2] Jevons, M. P., ibid., 1961, 1, 124.
[3] Rolinson, G. N., ibid., 1961, 1, 125.
[4] Knox, R., ibid., 1961, 1, 126.

the early days with the tetracyclines. At first strains resistant to the tetracyclines were exceptional, and it has been most unusual to observe the conversion of a sensitive strain to a resistant one during the treatment of a single patient. Yet resistant strains are now common. Dr. Jevons's celbenin-resistant strains belong to phage group III, a group characterized by the ease with which resistant strains develop. Some members of this group have also spread widely throughout hospitals, in many cases probably starting from small beginnings. That only a few staphylococci were originally concerned is also almost certainly true of the notorious type 80. If a similar epidemic staphylococcus was found to be resistant or was converted to celbenin-resistance a rapid expansion in numbers might be possible.

It would be a tragedy to lose such a valuable new drug by lack of forethought. There is a good case for restricting the use of celbenin in the same way as the prescribing of erythromycin was restricted. Indiscriminate use should be condemned, and this antibiotic should be reserved for serious infections for which sensitivity tests suggest its use, or in which a bactericidal effect is needed. It is also unquestionably the drug to use for severe acute infections, such as post-influenzal staphylococcal pneumonia, when treatment has to be started before laboratory studies can be completed. And, finally, if patients are found in hospital infected with or carrying celbenin-resistant *Staph. aureus*, they should be isolated both to protect other patients and to prevent the dissemination of yet another undesirable strain among the already too large collection of antibiotic-resistant staphylococci.

INFLUENZA DURING PREGNANCY

Women naturally worry about the possible effect of illness during pregnancy on their unborn children. Influenza is here again, being particularly prevalent in the Midlands (see p. 140), and many pregnant women will become infected. What answer is a doctor to give when he is asked the inevitable question?

It is now clear that environmental influences are important in the aetiology of most congenital malformations, and of course maternal infections are suspect. So far, however, only two have been unequivocally incriminated —rubella and toxoplasmosis—and it seems likely that for the great majority of malformations the aetiological factors will turn out to be connected with the internal environment of the uterus, with its blood supply and endocrine balance. Certainly there had been little reason to suspect influenza until 1959, when V. P. Coffey and W. J. E. Jessop[1] presented data to suggest that the Asian virus might not be entirely blameless. During the winter of 1957–8 they identified 663 women at Dublin antenatal clinics who said they had had influenza since they had become pregnant. Of the births to these women 3.6% were malformed, compared with 1.5% in the same number of paired controls. The commonest malformation was anencephaly.

A more recent study by R. Doll, A. Bradford Hill, and J. Sakula[2] has failed to substantiate these findings. In their investigation an almoner, experienced in medical research, interrogated 661 women who paid their first visit to the antenatal clinic at the Central Middlesex Hospital between November, 1957, and March, 1958. (Influenza caused by the Asian strain of virus A first became epidemic in Great Britain in the second half of 1957.) Of these women, 175 said they had had influenza since the summer of 1957 and remained under observation until delivery, when the infants born to them were specially examined for congenital defects. Nothing was discovered to suggest that the influenza virus was harmful to the foetus in the early months of pregnancy. These authors point out, however, that in Scotland (where each year data on stillbirths by diagnosis and month of occurrence are published) the number of anencephalic stillbirths for the eight months from May to December, 1958, was 39% higher than the average for the preceding eight years. Their conclusion is that, though in special circumstances infection with the Asian virus during the early months of pregnancy may possibly increase the risk of anencephaly, in general the hazard is a small one. Thus, to return to the doctor who is asked by a pregnant woman whether the influenza she is suffering from is likely to affect her child: he may without hesitation reassure her, secure in the knowledge that the risk, if any, is slight.

1 Coffey, V. P., and Jessop, W. J. E., *Lancet*, 1959, 2, 935.
2 Doll, R., Hill, A. B., and Sakula, J., *Brit. J. prev. Soc. Med.*, 1960, 14, 167.

HAZARDS OF IRON-DEXTRAN

Several years after the iron-dextran compound "imferon" had been introduced into clinical practice H. G. Richmond[1,2] found that intramuscular injection of it into the rat causes sarcomas to develop at the site of injection. A. Haddow and E. S. Horning[3] confirmed and extended these observations, and a leading article[4] in these columns discussed their implications for the treatment of patients. After reviewing the experimental work it noted that "we cannot affirm the hazard to man, let alone measure it," and suggested that the drug should be withdrawn "from any kind of general use in man," though it might have "a useful place in the treatment of such cases of iron-deficiency anaemias as are otherwise intractable in the elderly." The manufacturers of the drug (Benger Laboratories Ltd.), having previously, so we understand, ceased to advertise it in Great Britain, then suspended the sale of it "for general use, pending an independent re-examination of all the available evidence."[5] Benger Laboratories have now decided to advertise the drug again.[6]

In the nine months that have passed since the drug was withdrawn two case reports in which it was concerned have been published. Neither could be taken as confirming in man the carcinogenic potentialities of this drug in the experimental animal. In the first J. D. Crowley and W. J. S. Still[7] reported the occurrence of

a metastasis in the buttock, at the site of previous iron-dextran injections, from carcinoma of the cervix uteri. But the localization of metastases as a result of injecting other substances has also been reported, a recent case being that of a secondary growth from lung cancer at the site of penicillin injections.[8] The second case concerned with imferon was the development of what was reported to be an "undifferentiated sarcoma" in the arm at the site of previous injections.[9] No certain connexion of any kind between the tumour and the injections was established, and there is moreover a dispute about whether the tumour was in fact sarcomatous.[10] Meanwhile some distinguished signatories to a letter in this *Journal*[11] expressed their opinion that the use of imferon "in the clinical dosage recommended carries a negligible risk, and is probably less hazardous in other respects than intravenous iron preparations and blood transfusions." To this, Professor A. Haddow replied[12]: "I am, however, quite certain that no one is justified in asserting at the present moment . . . that the use of imferon in the clinical dosage recommended carries a negligible risk. From the nature of the case we cannot have a useful answer to this question under something of the order of 15 to 20 years. The statistics of the hazard (if indeed it exists in man) are quite unknown. We cannot therefore say it is negligible."

When the experts differ—as they often do in medicine—the practising doctor with his patient in front of him is in a quandary. He knows, as several of our correspondents have emphasized, that some risk of necessity attends many forms of treatment, and weighing the possible benefits against the possible risks often causes much anxious thought. In this case the facts are on record and have been interpreted variously. That a risk of carcinogenesis may attend the injection of iron-dextran is a view held by authorities in this field. As has been pointed out,[13] the long latent period between the injection of a potential carcinogen and the appearance of a tumour makes it impossible yet to measure the risk of iron-dextran in man; and it also may tend to encourage a sense of false security. Consequently, the selection of patients to receive this undoubtedly useful haematinic rather than another one is something that deserves special care. No doctor would lightly advocate the therapeutic use of a possible carcinogen unless all other ways of treating secondary anaemia had first been attempted. It is also worth bearing in mind that anaphylactic and other reactions to imferon have occasionally been reported, including fatalities,[14–16] but in this respect it may be less of a hazard than some other methods of raising the level of haemoglobin.

[1] Richmond, H. G., *Scot. med. J.*, 1957, **2**, 169.
[2] —— *Brit. med. J.*, 1959, **1**, 947.
[3] Haddow, A., and Horning, E. S., *J. nat. Cancer Inst.*, 1960, **24**, 109.
[4] *Brit. med. J.*, 1960, **1**, 788.
[5] Ibid., 1960, **1**, 890.
[6] See advertisement page 11.
[7] Crowley, J. D., and Still, W. J. S., *Brit. med. J.*, 1960, **1**, 1411.
[8] Worthy, T. S., and Wynne, E. J. C., ibid., 1960, **2**, 1208.
[9] Robinson, C. E. G., Bell, D. N., and Sturdy, J. H., ibid., 1960, **2**, 648.
[10] Golberg, L., ibid., 1960, **2**, 1598.
[11] Duthie, J. J. R., *et al.*, ibid., 1960, **2**, 234.
[12] Haddow, A., ibid., 1960, **2**, 663.
[13] Ibid., 1960, **2**, 659.
[14] *Registrar-General's Statistical Review of England and Wales for the Year 1958*, Pt. 3, Commentary, 1960, H.M.S.O.
[15] *Pharm. J.*, 1960, **184**, 379.
[16] Menon, M. K. K., and Willmot, M., *J. Obstet. Gynaec. Brit. Emp.*, 1960, **67**, 804.

ARSENIC AND LUNG CANCER

When considering known carcinogens in man's environment as causes of lung cancer, emphasis has generally been placed on the polycyclic aromatic hydrocarbons originating in partial combustion. More recently attention has been directed once more to the possible effects of arsenic, which, in the form of arsenious oxide, is present in both urban air and in tobacco smoke.[1] Its carcinogenic action has been well established both experimentally and as an occupational hazard in various industries. The amounts of arsenic in urban air are variable as are those in tobacco smoke, and the facts are still more confused owing to the difficulty of determining the total arsenic in a specimen. For example, in a fuel it is important to determine both the "volatile arsenic" and the "fixed arsenic."

W. E. Smith[2] gave evidence that concentrations of 1,000 μg. of arsenious oxide in 1 cubic metre of air can produce occupational lung cancer. F. Goulden and colleagues[3] reported values of a fraction of a microgram in the same amount of urban air. On the other hand G. Blodgett[3] has recorded 168 μg. per cubic metre in a laboratory building. H. S. Satterlee assumes that this background arsenic is related to arsenic metabolism and that it represents the arsenic expired (possibly as trimethylarsine) by the human occupants of the laboratory. He supports his supposition by the results of analysis of expired air from both smokers and non-smokers. The amounts of arsenic in tobacco smoke are very varied and are said to be due entirely to the use of arsenical insecticides used in tobacco plantations. This practice is declining now, but for American cigarettes the arsenic content increased approximately sixfold between 1923 and 1951. Only a fraction (up to 18%) of the arsenic in the tobacco appears in the smoke of a cigarette, which according to M. E. Daff and E. L. Kennaway[4] contains about 7.5 μg. Later E. C. Cogbill and M. E. Hobbs[5] found much smaller amounts (1.4 μg.).

It has been suggested that arsenic taken into the body regularly by various routes is always appearing in the lungs as the metabolic product trimethylarsine and that the combined effect of arsenic with other carcinogens may be critically important in carcinogenesis. Arsenic in varied concentrations with carcinogenic tars has been shown to have a critical catalytic effect in animal experiments,[6] and it may well have a similar effect in human bronchial carcinogenesis. Recent studies of the arsenic content of bronchial mucosa and submucosa in man[7] have revealed higher amounts in the tissues of lung-cancer victims than in those of patients who died from other causes. Trace quantities of other mineral substances such as chromium and nickel known to represent an occupational hazard have been detected in tobacco by Cogbill and Hobbs,[5] but they were unable to show any transfer to the smoke. It appears that the recent suggestion by W. Sunderman[7] that nickel in tobacco

[1] Satterlee, H. S., *New Engl. J. Med.*, 1960, **263**, 676.
[2] Smith, W. E., *Acta Un. int. Cancr.*, 1953, **9**, 476.
[3] Goulden, F., Kennaway, E. L., and Urquhart, M. E., *Brit. J. Cancer*, 1952, **6**, 1.
[4] Daff, M. E., and Kennaway, E. L., ibid., 1950, **4**, 173.
[5] Cogbill, E. C., and Hobbs, M. E., *Tobacco Science*, 1957, **1**, 68.
[6] Coulon, A. de, *C.R. Soc. Biol. (Paris)*, 1925, **93**, 1369.
[7] Sunderman, W., *Brit. med. J.*, 1960, **2**, 1230.
[8] Kennaway, E. L., ibid., 1954, **2**, 663.

smoke is a carcinogenic hazard requires much more experimental support before it can be regarded seriously.

However, it would be wrong to ignore the presence of minor carcinogens even if they are present in man's environment in small and decreasing amounts, for they may have co-carcinogenic or catalytic effects. The interpretation of findings of this kind has been very fully discussed by Kennaway,[8] who was of the opinion that no carcinogen, even in sub-threshold concentration, should be regarded as negligible.

WHITHER B.C.G.?

B.C.G. vaccination has now been available in this country for eleven years. First imported from Copenhagen in 1949, it was issued originally to vaccinators approved by the Ministry for the intracutaneous vaccination of nurses, medical students, and contacts of tuberculous patients. Simultaneously a trial of its efficacy was organized on 60,000 schoolchildren by the Medical Research Council; the latest report from this trial shows an 83% protection which was still effective after five years.[1] In 1953 vaccination was extended to include 13-year-old schoolchildren; this was subject to Ministry approval of the scheme submitted by each medical officer of health, who was also given the responsibility of appointing the vaccinators. All members of hospital staffs were added in 1958, and older schoolchildren and university students in 1959. Apart from a few special trials, these are the only persons authorized to receive official vaccination.

Any protest against restricting the use of B.C.G. to certain persons and to chosen doctors was cut short in 1957 by the release of Glaxo freeze-dried vaccine on the open market. Views on the official policy of restricting non-contact vaccination to students over the age of 12 are divided. While some contend that there is no point in a further extension until the existing scheme is fully implemented, others such as T. M. Pollock have suggested lowering the age to 10, as by 13 years up to 40% were already positive reactors; he also pointed out that 0.23% of the 14-year-old children in the M.R.C. trial were unsuspected cases of tuberculosis.[2] M. I. Griffiths and W. Gaisford[3] supported this view, pointing out the risk of genital tuberculosis in girls after a flare-up of their primary infection at puberty and went on to suggest that the optimal age may be infancy. Much depends on how long a single vaccination remains effective. The difficulties of infant vaccination are mainly associated with the intracutaneous route; Griffiths has suggested that these may be avoided by using multiple-puncture vaccination.[4] The effectiveness of this simpler method is now being studied in schoolchildren by the British Tuberculosis Association.

The more ardent supporters of B.C.G. would convert the world to tuberculin-positive by vaccination: its more extreme opponents, deploring the loss of the diagnostic tuberculin test, would strive for a tuberculin-negative herd. A. H. Griffith has shown that compromise is possible. In Cardiff all schoolchildren are tested annually to discover positive reactors and trace sources of infection, but those who are still negative on reaching the age of 13 are vaccinated.[5] Nevertheless at some point in the decline of tuberculosis there is likely to be a move to end B.C.G. vaccination, so we should be wise to consider the implications of controlling tuberculosis in a tuberculin-negative population. Ideally it would mean that every converter must be discovered, isolated, and treated before he can develop open tuberculosis; this can be done only, as our veterinary colleagues have shown, by the regular tuberculin-testing of the whole population. We should do well to calculate in advance the immensity of this task before too readily abandoning the simpler procedure of B.C.G. vaccination.

[1] M.R.C. Tuberculosis Vaccines Clinical Trials Committee, *Brit. med. J.*, 1959, **2**, 379.
[2] Pollock, T. M., ibid., 1957, **2**, 20.
[3] Griffiths, M. I., and Gaisford, W., ibid., 1956, **2**, 565.
[4] —— ibid., 1960, **2**, 1116.
[5] Griffith, A. H., *Roy. Soc. Prom. Hlth J.*, 1960, **80**, 76.

CATARACT INDUCED BY CORTICOSTEROIDS

Recently the formation of cataract in patients receiving large doses of corticosteroid has been described.[1] The cataracts were of a very specific type, occurring just in front of the posterior lens capsule in the axial region (posterior polar). Furthermore, they appeared to remain localized to this region. The appearances described are quite different from those of senile cataract but resemble more closely the cataracts which may result from the ingestion of toxic agents. Similar cataracts may occur after the lens has been exposed to radiotherapy or to infra-red irradiation.

Such posterior cortical cataracts appeared in seventeen of forty-four patients with rheumatoid arthritis who had had prolonged corticosteroid treatment. Nineteen patients suffering from rheumatoid arthritis, but who were not receiving corticosteroids, were also observed. In none of these were posterior cortical cataracts found. Furthermore, in the group of forty-four patients treated with corticosteroid there was no case in which cataract formed when the dosage was under 10 mg. of prednisolone (or its equivalent) daily. No changes in the lens were observed in any patient who had not had continuous corticosteroid therapy for at least one year. It appeared also that the higher the maintenance dose and the more prolonged the treatment, the more likely were posterior cortical cataracts to form.

It would seem, therefore, that the danger of developing cataracts as a result of corticosteroid therapy is minimal unless treatment is prolonged and the dosage high. There have been no other reports of cataracts occurring as a result of the administration of corticosteroid, and the possibility of cataract formation does not appear to be sufficient justification for withholding treatment with steroids when it is indicated. The mechanism of the production of the lens opacity is unknown, but the lesions seem to progress very slowly and vision is not affected at any rate in the early stages. It is well to bear in mind the possibility of cataract formation, however, and to examine at regular intervals the eyes of patients receiving steroids in high dosage for a long time.

[1] Black, R. L., Ogelsby, R. B., von Sallman, L., and Bunim, J. J., *J. Amer. med. Ass.*, 1960, **174**, 166.

MEDICAL SERVICE WITHIN THE COMMONWEALTH AND OTHER COUNTRIES OVERSEAS

BY

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1. The following communication, in the main, embodies a new deal for doctors going from the United Kingdom and other Commonwealth countries to serve for a period in the developing countries within the Commonwealth and also outside it. The biggest contribution which employing authorities, such as regional and hospital boards, universities, and general practice, can make is in applying a code of secondment and in treating a period of overseas service as an asset to promotion prospects in the medical services rather than the reverse. Acknowledgment is made to the Commonwealth Education Conference, and the Ministry of Education (Circular 10/60, 1960) for many of the ideas concerning recruitment of teachers for overseas that have been incorporated herein.

The Challenge

2. All look forward to the day when the greater part of the traffic of medical officers within the Commonwealth (and other countries) will be on the basis of full reciprocity, and when each country will be able to develop its own medical services to a point independent of outside help. However, at the present time short-term assistance is required by the underdeveloped countries both in the training and in the supply of medical personnel and auxiliaries, which needs are complementary. In order to ensure that the resources available are used to the best advantage, it is recommended that efforts should be diverted primarily to (*a*) filling some key posts in developing countries with personnel from other countries more favourably placed, and (*b*) training in the latter countries postgraduate and undergraduate students who would themselves fill key posts on their return to their own countries.

3. The Commonwealth, and particularly the United Kingdom, has both an opportunity and a duty to help, not only on grounds of humanitarianism and brotherhood, but as part of a policy leading to the further development of the Commonwealth idea and all that that implies. The Government of the United Kingdom (and other favourably placed governments such as those of Australia, Canada, and New Zealand) should offer more undergraduate and postgraduate places at university and technical level, with bursaries for the students filling them. On the supply side the Government should stimulate the recruitment of United Kingdom medical officers for service overseas and, in particular, should take financial and other measures to encourage recruitment. Apart from university posts, the need is largely for general-duty officers, both in hospitals and in polyclinics, on short-term contracts for from two to five years.

4. In addition to the Commonwealth, the continuing needs of foreign countries must be borne in mind. It is very much in this country's interests to help some of the countries which are trying to build up their medical services and wish to recruit British doctors—for example, Iraq, Persia, Sudan, Egypt, Colombia, Indonesia, etc.

The Difficulties

5. The call to give help comes at a time when there is a substantial shortage of doctors to meet the immediate needs of the people of the United Kingdom. At the present time many foreign nationals are employed as house-officers and registrars in the non-teaching hospitals owing to the shortage of suitable British personnel, and the Willink Report has induced a climate of retrenchment rather than of expansion of the numbers to be medically trained in this country. Notwithstanding this position, however, a small number of recruits to the key posts of the medical services overseas would represent an accretion to the strength of such services that could make an impact out of all proportion to the number involved, whereas such a number in the United Kingdom is marginal in relation to the total; it should be remembered that in the United Kingdom there is 1 doctor to 900 of the populace, whereas in Uganda it is 1 to 18,000; in Tanganyika, 1 to 22,000; and in Ghana, 1 to 25,000.

6. It should be possible to find some additional doctors by a redeployment or a stimulation of existing efforts. A substantial number of doctors have been going annually to take up posts in the Commonwealth overseas, but most of them have gone to one or other of the older independent countries. There will always be scope for exchange schemes and other forms of two-way traffic within the Commonwealth, but it is hoped that these countries will recognize that their need to recruit doctors from the United Kingdom is now *less urgent* than that of the developing countries.

7. Perhaps the main difficulty lies in giving doctors a feeling of confidence that if they serve for a period overseas their interests will be safeguarded before, during, and after their service, and they and their families will receive recognizably fair treatment. Examples are as follows:

(*a*) Expatriates overseas lose their place in the queue for promotion. The "out of sight, out of mind" attitude unfortunately prevails.

(*b*) Expatriates are not given time in which to apply for posts in the United Kingdom. Examples which can be culled from the medical press are of regional and hospital boards who require only two to three weeks for the receipt of applications after the appearance of the advertisement.

(*c*) Facilities for interview of short-listed applicants who are expatriates are almost non-existent. Indeed, in several cases the short-listed applicant has been out of pocket to the tune of several hundreds of pounds. Further, the fact that an applicant is an expatriate has on occasion militated against his being short-listed.

(*d*) If an expatriate is successful in obtaining a consultantship in the United Kingdom, no matter his seniority or high professional status overseas, he can only be credited with a maximum of four years' seniority with the National Health Service, and that as a matter of grace.

8. Although some provision for the continuation of technical aid by the transference of Commonwealth Development and Welfare Funds, etc., to emergent colonial territories has now been made, territories such as Ghana have been cut off without any continuing assistance such as they enjoyed when dependent territories. This would seem harsh.

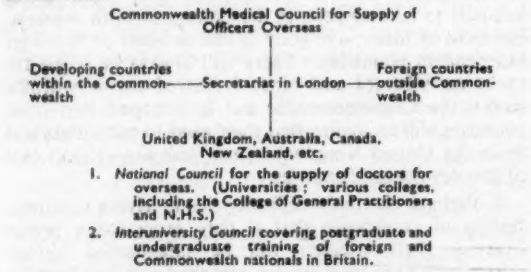
Measures Proposed

9. A fresh examination must be made of the needs of the medical services in the developing countries, so that

the extent of the problem can be assessed. Concurrently, an investigation into the needs of doctors going overseas, and into the difficulties of regional and hospital boards and universities in releasing them and in giving a firm undertaking about re-employment on return, must be instituted.

10. These investigations, which together should form an integrated scheme, should incorporate: (*a*) A Commonwealth medical council for the supply of officers overseas, with a secretariat in London. (*b*) National councils in the various countries of the Commonwealth. (*c*) A code of secondment. (*d*) A code for terms of appointment overseas. (*e*) Special allowances to augment where necessary the emoluments provided by the overseas employer and to cover additional expenses incurred in going and living overseas. (*f*) Terminal grants at end of contract, to provide a lump sum on return to this country. (*g*) A fund to assist doctors to return to the United Kingdom (or native country) for interview if they are short-listed for posts due to fall vacant at about the time that their overseas service will end.

The main outline of the above is given schematically as follows:


Commonwealth Medical Council for Supply of Officers Overseas
Developing countries within the Common-wealth
Secretariat in London
Foreign countries outside Common-wealth
United Kingdom, Australia, Canada, New Zealand, etc.
1. National Council for the supply of doctors for overseas. (Universities; various colleges, including the College of General Practitioners and N.H.S.)
2. Interuniversity Council covering postgraduate and undergraduate training of foreign and Commonwealth nationals in Britain.

11. A Commonwealth Medical Council for the Supply of Officers (and Auxiliary Personnel) Overseas

(*a*) It would seem essential that some central machinery be instituted through which the interested bodies can regularly discuss common problems, work out solutions, and co-ordinate action. The Council will bring together the main partners concerned in recruitment and resettlement. It will not itself undertake recruitment but will assist recruitment in a variety of ways and seek to promote a climate of opinion in which a period of service is regarded as an asset by the various employing authorities in the constituting countries. As the Council's terms of reference are in the field of policy-making and inspiration, and are to be likened to the Crusades of former days, it would perhaps be appropriate to suggest the President of the British Medical Association as its Chairman and instigator. Other members would be representatives of other Commonwealth countries, including the Presidents of the various Royal Colleges.

(*b*) Initially, a secretariat consisting of a full-time secretary and staff should be instituted in London. The duties will be the bringing together of the interested parties, and the implementation of the policy of the Council so that secondment to underdeveloped countries and training of nationals from these latter countries may be expedited.

12. National Councils for the Supply of Officers Overseas

Such councils will co-ordinate policy and action at the national level and will be constituted by representatives of the Ministry of Health, the universities, and the various Royal Colleges, including the College of General Practitioners and other interested bodies. Initially, the secretariat mentioned in 10 (b) may be used in the United Kingdom.

In the United Kingdom the National Council should co-operate with the Inter-University Council for Higher Education and the British Postgraduate Medical Federation with a view to co-ordinating the training of Commonwealth and foreign nationals in this country in the field of postgraduate, undergraduate, and technical education.

13. A Code of Secondment

This should be a code of the terms which would allow the release of doctors for service overseas and their re-employment on return. It is suggested that the code should embody the following proposals:

(*a*) The employing body will second the doctor concerned for a period of two to three years (with possible extension up to six years), and will undertake at the end of that period to secure his reinstatement, if desired, in his former post or a post comparable to it, with consequential increase in salary and promotion in accordance with the passage of the years overseas.

(*b*) Where a doctor on secondment while still overseas applies for a post, his application will be considered fairly without interview on the basis of reports obtained from his former employers and also his overseas employer, on equal terms with applicants who are available for interview, unless the doctor's absence has greatly exceeded three years.

(*c*) In the case of senior posts, such as consultantships in the National Health Service and university senior lectureships, the applicant, if short-listed, should be assured of a return passage for the interview (by air).

(*d*) Although employers in this country will attempt to reinstate the returned doctor in his former post or one comparable to it (with due incremental salary or promotion consistent with the passage of the years), it may be impossible to guarantee this. Until this is done the returning doctor should be guaranteed for a period of up to two years the salary (with due increments) he would have been receiving had he remained in this country throughout.

14. A Code of Terms for Applicants Overseas

The code of secondment suggests ways in which employing authorities in the United Kingdom may help doctors before, during, or after his service overseas. It is no less important that the overseas employer should play his part by providing satisfactory conditions, both personal and professional, while the doctor is in his overseas post.

The United Kingdom cannot directly exercise control over employers in other countries, but the Commonwealth Medical Council should be able to help by drawing up a code as a guide both to the doctor and to the overseas employer, setting out the points that ought to be covered in contracts and conditions of appointment, and the points on which information should be available to doctors before they accept appointments.

Particular subjects which come to mind are: (*a*) Up to date and accurate estimates of the cost of living. (*b*) Guarantees of free time and facilities for research in the case of university personnel. (*c*) Specific arrangements for housing doctors' families and accurate assessment of the local facilities for education. If the latter are deficient, generous allowance for the education of children in the United Kingdom (or native country) and arrangements for annual leave to the United Kingdom of family (by air). (*d*) Possible special allowances to cover expenses incurred in going and

living overseas. (*e*) Possible terminal grants at the end of contract. (*f*) Generous but clearly defined contracts concerning money allowed to be sent back to this country and generous income-tax arrangements such as are enjoyed by United Nations personnel.

Conclusion

15. Many authorities in this country are endeavouring to stimulate recruitment among doctors for overseas service, and many hospitals, both teaching and non-teaching, are helping in the training of Commonwealth and foreign nationals.

Due acknowledgment of the very fine efforts of the Missionary Societies, W.H.O., the British Council, the universities, the Inter-University Council for Higher Education Overseas, the Overseas Committee of the B.M.A., the Overseas Medical Service, the Overseas Settlement Bureau, the British Postgraduate Medical Federation, the various Royal Colleges, and the various regional and hospital boards is hereby given. However, their efforts are not enough and are extremely uncoordinated.

16. It would seem that some impetus should be given at a high level so as to infuse nationally a spirit of service and dedication to Commonwealth development, so that service overseas (as of yore) was part of the pattern of the national life, as reflected in Medicine. To do this it is felt that a crusade should be started with its head the ex-president of the B.M.A., the Duke of Edinburgh, and its convener, the present President, with the co-operation of the Presidents of the various Royal Colleges.

Medical practice overseas means more than giving essential services to developing countries; it embodies the development of a culture which, dearly wrung from the past centuries, may afford a signpost for a new world.

APPENDIX A—A CODE OF SECONDMENT

17. Universities

Universities may second under various schemes which are inter-related.

(*a*) By the provision of supernumerary personnel to departmental staffs so that there may be a procession of lecturers to similar departments overseas. This would remove the fear of insecurity with regard to promotion and re-employment on return to this country. This was recommended by the University of London in 1951 but has never been implemented.

(*b*) By secondment from within the existing establishment of university departmental staffs. This has already been done at the Royal Free Hospital School of Medicine by appointing two lecturers at the same time for a combined lecturership to be held at the Royal Free and at University College, Ibadan. One candidate has proceeded to Ibadan for two years and the other works in London; after two years they interchange; on the fifth year they both work in London. Because of the numbers of staff employed and long-term planning of similar secondments overseas, no difficulty will be experienced in the re-employment of the "extra" lecturer returning for the fifth year.

(*c*) Proleptic appointment: It would seem appropriate with quinquennial estimates formulated some years ahead to arrange for the redeployment of members of the existing staff who have been earmarked for promotion. For example, a junior lecturer who has all the hallmarks of the future senior lecturer within the department may be seconded overseas for two to three years prior to his promotion to that post which has been proposed and accepted within the quinquennial estimates. There should be no difficulty in filling his lecturer's post in the interim.

(*d*) Universities may adopt universities in the developing countries *in loco parentis*. This is already taking place in the American sphere of influence—for example, Indonesia—and also in the British—for example, Birmingham and the University of Rhodesia and Nyasaland. Further, departments can adopt departments *in loco parentis*. This is being done partially at the Great Ormond Street Hospital for Sick Children, which regularly sends a registrar to Makerere College, Uganda.

18. Hospital Service

Although a scheme is in existence for the secondment of N.H.S. personnel to countries overseas, in only a few instances have these facilities been taken up. The reason for this is the general climate of insecurity mentioned in paragraph 7, and the reluctance on the part of regional and hospital authorities to concern themselves with matters other than those within their immediate sphere of influence.

It would seem that if there was a spirit of real endeavour to help within the N.H.S., such as is at present inspiring the Ministry of Education in this country (Appendix B), then modifications of secondment (supernumerary and within the establishment), proleptic appointment, and adoption *in loco parentis*, as is suggested for the universities, may be effective.

19. General Practice

At present in this country it would seem that the pattern of recruitment for general practice is the appointment of trainee general practitioners immediately after the pre-registration appointment of newly graduated doctors. It would seem not unreasonable if newly qualified doctors may be allowed to serve a period of two to three years after pre-registration in polyclinics or in hospitals overseas. This would gain support if they were assured of posts on their return to this country.

Although it may be said that these newly qualified doctors are inexperienced, this is only relatively so, and the situation should be judged on the grounds that the needs of the developing countries are desperate.

The overseas countries would be helped until such times as they have sufficient of their own nationals to man their own services, and British medicine would be the richer on the return of those young doctors after a period overseas.

It is suggested that recruitment for general practice may be organized under the aegis of the College of General Practitioners so that there is a "pool" of young postgraduate general practitioners either serving overseas or having returned to this country after a period overseas. Admittedly the difficulties embodied in this proposal are many, but they are not impossible of solution.

APPENDIX B

20. The Commonwealth Education Conference held at Oxford in 1959 drew attention to the shortage of teachers in some Colonial territories and other developing countries of the Commonwealth.

In 1960 the Ministry of Education allocated a sum of £700,000 annually for the recruitment of 400 teachers for overseas and instituted a National Council for the Supply of Teachers Overseas (in conjunction with similar authorities in Scotland and Northern Ireland). In 1960 Circular 10/60, incorporating details of a

suggested Teaching Service in the Commonwealth and other countries, was published.

Much of the material covering this memorandum on the proposed "Medical service within the Commonwealth and other countries overseas" has been based on this Ministry of Education Circular 10/60. Acknowledgment with thanks is here given.

POSTGRADUATE EDUCATION IN THE FIELD OF RHEUMATISM AND ARTHRITIS IN THE U.S.A., 1960

BY

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This review is based on a period of four months in the U.S.A., spent for the most part at Bethesda by invitation of the National Institute of Arthritis and Metabolic Diseases and with visits to research centres and university departments of medicine in Washington, Pittsburgh, New York, Baltimore, Durham, Birmingham, Dallas, New Orleans, Boston, Cleveland, Chicago, and Los Angeles, undertaken with the assistance of the Wellcome Research Travel Fund and the centres concerned.

Comparison with the educational programme in Great Britain must take into account two major differences between the countries: firstly, the rather different structure of undergraduate and graduate education in the two countries; and, even more important, the very great difference between the two countries in the organization of medical services to the public.

Undergraduate and Graduate Education

Before receiving a doctorate of medicine, the American student has usually spent four years in university and four years in medical school: his school-days have not in general resulted in as quite a high level of education as do English private schools, but this difference is made up by the time of entry to medical school. After the M.D. examination he may spend a year as an intern (house-physician) before taking his State examination. For intending specialists there follows five years' training in an approved centre or centres before he is allowed to take his specialty board examinations (corresponding to our M.D. or M.R.C.P.). This is made up of two to three years as resident (registrar) and then two to three years as a research fellow or in specialty practice. The 19 specialty boards are composed of representatives of the American Medical Association and of the National Specialist Societies. There is no specialty board in rheumatism, which is included mainly with the specialty of internal medicine. Although many members of the American Rheumatism Association do not have specialty board qualifications at all, a number possess these in the fields of internal medicine and a few in the fields of physical medicine, pathology, or orthopaedic surgery.

A specialty board qualification is not necessary for appointment to academic or hospital posts, particularly in the more renowned centres, but it is desirable in any event and usually necessary for appointments to smaller hospitals, etc. There are large differences between the calibre of students accepted at different universities, but in general the just-qualified M.D. is probably similar to his M.B., B.S. counterpart in England, knowing perhaps a little less of clinical evaluation and a little more of laboratory diagnosis. Demand for doctors as a whole is increasing fast because of the increase in population.

Organization of Medical Services

The second major difference between the two countries is in the organization of care. In England this is a Government responsibility; in the States, consultant services are sponsored by individual consultants themselves (private practice) often with part-time hospital appointments, by private hospitals and clinics, by private or State university hospitals, and by Government agency only in small part (in the Veterans Administration Hospital and the Public Health Service). The majority of consultants are therefore chosen by private hospital or university boards, and there is no overall control of specialty categorization or of the numbers of specialists in any one specialty field or in any one area. In this system of private enterprise, therefore, the outlet for specialists in any particular field depends primarily upon demand and usefulness.

Rheumatism has become very much more important over the last 10 years as a specialty field: although not being rigidly defined, the university specialists are usually to be found within the department of medicine, but they may also be in paediatrics, pathology, or biochemistry. Thus membership of the American Rheumatism Association has increased from 876 in 1955 to 1,283 in 1959. In 1960 there are 1,350 members in 44 states. These numbers are related to a total population of 180 million and a total medical population of 210,000. In 1955, American Rheumatism Association members were found in 40 of the 48 States (as well as in D.C., Puerto Rico, and eight Canadian provinces) and in 228 cities within the United States. Some centralization in New York was inevitable (112 out of 876 members were listed therein in 1955). There are now active rheumatism units in most of the 86 universities of the U.S.A.: 45 of these are in receipt of research training grants from the National Institute of Arthritis and Metabolic Diseases (as well as some other hospitals, such as Mount Sinai, New York), as compared with six in 1946. In view of the ever-increasing funds voted by Congress for expansion in this and other fields, it is clear that there is and will continue to be many posts available in the U.S. over the coming years for people well trained in the field of rheumatism and arthritis.

By contrast, in Great Britain, with its more rigid and centralized control of consultant appointments, the great advances made in the rheumatism field have not been reflected in the recognition for appointment purposes of specialization in this area of the field of internal medicine. There tend, therefore, to be few entrants for training in this field, and they are correspondingly difficult to place when their training has finished. Many of them emigrate, some find appointments in physical medicine, and a few find posts, against very strong opposition, in general medicine. In most universities and hospital centres, rheumatism patients are bandied between the orthopaedic surgeon, the medical consultant, and the physical medicine consultant, whereas in the U.S.A. the rheumatologist,

a consultant in internal medicine with as good a background in that subject as his "internist" colleagues, takes overall responsibility for these chronic diseases. As a result, the general level of medical care in the rheumatism field in England is low apart from a few specialized centres.

As an *ad hoc* programme, therefore, the need in the United Kingdom for postgraduate ("refresher") education is great. However, as will become evident during the ensuing review, the long-term remedy for the inevitably continuing deficiency in this and other fields is to educate postgraduates either immediately after graduation or in the pregraduate stage. Education of established consultants is nowhere as rewarding or as economical as adequate education during earlier stages and the inculcation of a habit of continued study.

In the field of rheumatism, which lies mainly within the specialty of internal medicine, overlapping slightly with physical medicine and rehabilitation, postgraduate education in the U.S.A. is vigorous and far-sighted. It depends, as in all other specialties, primarily on individual apprenticeship during hospital *residencies* (registrarships). This is true also in England. In addition to these regular hospital training posts, which allow the acquisition of practical clinical wisdom and at the same time maintain the hospital, education in this field is furthered by *fellowships and traineeships in research*, by *"refresher" courses* or postgraduate courses, and by *symposia* and *society meetings*.

Residency Training

During his two to three years' residency, the doctor takes on progressively more and more clinical responsibility, so that in many American hospitals the residents, at least in internal medicine, appear to be primarily responsible for the care and treatment of the patient—with advice and comments on the daily or twice-weekly ward visits from the visiting consultant. The latter may be a professor of medicine or of public health, or a specialist in some field such as allergy or cardiology, or someone who is primarily a biochemist. Other residencies rotate through various services and others still may be allocated to specialty clinics. As might be imagined, supervision is very variable, and residents may well be trained or "do-it-yourselfers." Experience in rheumatism and arthritis is therefore acquired in the general framework of internal medicine, and particularly in those centres where energetic arthritis units exist. Fortunately these are becoming increasingly common, and exist in most of the university centres of the U.S.A.; and, just as many of the younger specialists owe their interest in this field to their residency days in such old-established centres as Harvard, Columbia, New York, or Ann Arbor, so in the future such interest will be stimulated by the full-time directors of arthritis units in these many university hospitals.

Research Traineeships and Fellowships

After his resident years, the man seeking board recognition as a consultant must put in the remainder of his five-year training period in clinical specialty practice or research. Those seeking an academic career usually apply for research fellowships or traineeships at a recognized centre. While formerly there were comparatively few centres where a training in arthritis and rheumatism was possible, and comparatively few fellowships available, now, as the result of the increased Governmental expenditure in public health, both the number of centres capable of undertaking training and the number of trainees supported has increased remarkably. In addition to direct research fellowships and traineeships supported by the Arthritis and Rheumatism Foundation and the National Foundation, the Helen Hay Whitney Foundation, and the Public Health Service, the U.S. Public Health Service has instituted a series of training grants for the setting up of research and teaching units on a large scale. These have altered the climate of the university hospital centres a great deal.

For instance, out of the 185 training grants made for 1959 by the National Institute of Arthritis and Metabolic Diseases, 47 are listed for arthritis alone and total $913,286, or £325,012. They are distributed among 42 centres, of which only one is outside continental U.S.A. (Puerto Rico). Thus the average grant is $21,743 a year and lasts usually for a period of five years. (Seven centres receive more than $35,000 each.) The typical structure of a unit allowed by such support is an honorary director (professor or assistant professor paid usually by the university entirely), salaries for one or two trainees and a technician, sometimes a secretary, equipment, and a fund to pay visiting lecturers. Such a unit is often also in receipt of funds from elsewhere—for example, the Arthritis and Rheumatism Foundation or the National Foundation—allowing still further personnel. These public health training grants are for the express purpose of training academically inclined personnel for basic research and clinical investigation so that later they will attain university posts in this or related fields.

In a typical centre the trainees attend ward rounds and conduct clinics, but spend most of their time on their research project for a two-year period. Already a large number of such trainees have obtained university posts, and in their turn have started arthritis units with the aid of such training grants. Others have left for private consultant practice. This seems an ideal form of postgraduate education, ensuring not only education of the trainee but future training of others in this field within the university framework.

Comparison with the British scene reveals the great difference between the countries in this phase of education in rheumatism. Perhaps the major comparison that can be made is that the National Institutes of Health budget for 1960 was $400m. (already raised by the Senate to $600m. for 1961) as against a budget of £3–4m. for the Medical Research Council. In more detail, the National Institute for Arthritis and Metabolic Diseases has itself a budget of $39m. in 1960, having risen from $30 m. in 1959, $25m. in 1958, and $15m. in 1956. In England, Wales, Scotland, and Northern Ireland there are fewer than a dozen units to which research or clinical trainees could be apprenticed, and these are variable in calibre. This represents about 7 of the 15 British universities. It is difficult to compare the number of trainees, but at a guess there are about 100 in the U.S. Public Health training grants and traineeships combined, plus about 30 fellowships and 30 traineeships given yearly by the Arthritis and Rheumatism Foundation. In England there are a few (? five) research fellows in this field sponsored directly by the Medical Research Council and a few by the Empire Rheumatism Council. Some of these are non-medically qualified biochemists awaiting university posts

and interested primarily in, for example, polysaccharide chemistry.

Most of the research and clinical trainees in the English units come from and go back overseas. Thus at Taplow over the past 10 years we have had 32 research fellows over and above the resident and permanent research staff: only eight of these were British. British fellows wanting training are few and the facilities are very limited. This is to a large extent due to the fact that university and hospital posts in Britain for people trained in this field are still lamentably few in comparison with the U.S.A.

Postgraduate Courses ("Post-doctoral")

The postgraduate course is the traditional British mode of teaching postgraduates. In the U.S.A. postgraduate courses in the rheumatic disease field are held regularly in New York, and from time to time elsewhere. Thus in 1958 17 courses in arthritis and rheumatism were listed (eight in New York, others in Buffalo, Chicago, Ohio, Los Angeles, Mayo Clinic, New Orleans). They were to last on average two to three days, although one course lasted a full week and another one comprised one session a week for two months. Some last only one day. This is against a total yearly background of 975 postgraduate courses under 42 listed categories held by 212 organizations. These courses were intended for physicians in established practice, and cost anything from 30 to 100 dollars. The subjects covered were wide. In most of these courses the speakers are for the most part those staffing the local centre or hospital, with a few guest speakers of renown* whose expenses or honorarium are paid out of subscriptions, often with the help of a grant from drug companies, from the Arthritis and Rheumatism Foundation, or in some instances out of public health training-grant moneys. British postgraduate courses differ only because attendance by whole-time specialists in a National Health Service is paid for (as well as travelling and living expenses) by the National Health Service. In the U.S.A. tax deduction for the expenses of attending is allowed.

In both the United States and Great Britain exhibits aimed at the practising physician are put on at medical meetings, and a bulletin on rheumatic disease is circulated by each national rheumatism society.

Symposia

Symposia represent education at its top level where generally the frontiers of knowledge are explored by a small group of experts intimately concerned in advancing those frontiers. Because the population of the States is three to four times that of Great Britain, because relatively more people within the medical fold are also engaged in "basic" research (to use the current shibboleth), and also because the more generous funds usually allow for distinguished foreigners to attend, these symposia appear on average to be more numerous than those in England. They fulfil the same purpose, however, and are run on much the same lines as those in Great Britain, and need not be further discussed except perhaps to remark that official National Institutes of Health participation occurs in the U.S.A. in addition to support by private foundations, drug firms, universities, hospitals, medical schools, and professional associations such as the American College of Physicians, whereas the Medical Research Council has not so far taken an active part in such colloquia, which are run by such bodies as the Royal Colleges, the Royal Society of Medicine, the Ciba Foundation, etc.

*However, in a full week's course held in January, 1960, under the auspices of the American College of Physicians at Cornell, New York, there were 14 guest speakers as well as 25 from Cornell itself.

Undergraduate Training Grants ("Pre-doctoral")

As stated above, this survey has led to the endorsement of the view that education is the more valuable the earlier it is received. The "basic" problems in this field are no different in kind from those encountered elsewhere in medicine: besides the problem of therapy and its advancement of diagnosis, of social care, and of prevention, education for the future must include acquaintance with mechanisms (biochemistry, immunology, epidemiology and methods, biophysics, statistics). In Great Britain the medical student has very little acquaintance with this group of very common diseases largely because his teachers are concerned mainly with other fields and comparatively infrequently include anyone with both interest and qualifications in this field. The new U.S. Public Health training programme for clinical investigators is therefore of great interest, since it aims at the medical student (pre-doctoral).

As an example, I may cite the scheme at Duke University, sponsored by the U.S. Public Health Service, together with the Commonwealth and Markle Foundations, the American Cancer Society, and Duke University. This project takes selected medical students for a nine-months period with intensive training in concepts and experimental methods in cell biology, followed by directed research and special didactic cases in biostatistics, electronics, genetics, embryology, mathematics, and logic. For this purpose new staff members have been appointed to the University and a new wing has been added. By rearrangement of the ordinary course no time will be lost in graduating.

National Institutes of Health

Finally, to complete the picture of postgraduate education in the U.S.A., the National Institutes of Health at Bethesda must be briefly mentioned. The National Institute of Arthritis and Metabolic Diseases, besides running the extramural programme of training grants already referred to, as do each of its six sister institutes, plays a leading part in education within the field of rheumatism and arthritis. Under the clinical direction of Dr. Joseph Bunim and the general administrative direction of Dr. Daft (with Dr. R. Knutti covering the extramural programme), workers in this field have made a large number of fundamental advances in the past 10 years and have trained a large number of highly selected young men, both in the clinical and in the laboratory field, and, even more important, young men skilled in both aspects of research. These are now beginning to head up university departments all over the country.

The National Institutes of Health have two special organizational advantages over and above their unique facilities and their top-rank staff: firstly, fellows can get their period of compulsory military service done as trainees there; and, secondly, patients are treated without charge—thus ensuring a wide selection. With its intimately associated laboratories and hospital accom-

modation, it offers a first-class opportunity for this modern synthesis of clinical and laboratory approach. The Medical Research Council in contrast has its clinical units scattered in various centres throughout the country, and its central laboratories at Mill Hill are without close clinical opportunities. Nevertheless, considering its relatively restricted budget, it seems (on rather short acquaintance with U.S. conditions) that the rapport between clinical and scientific staff is just as good in a small M.R.C. unit situated within and in close liaison with a university medical school as in the vast corridors of the National Institutes of Health. Indeed, one of the practical difficulties of the National Institutes of Health was that of knowing what was going on one floor above or below. Knowledge from related fields and from association, which is highly important for education, may demand a certain maximum size, and it might be considered that the policy of the Medical Research Council—to establish clinical units in relation to existing university centres or to existing hospitals allied to a university or other scientific centre—is better for this smaller country than the erection of Bethesda-like institutions.

Conclusions

Postgraduate education in rheumatism in Britain is badly needed if we are to keep pace with scientific development and practical applications as exemplified in the American scene. Some expansion of training facilities is needed, but this is useless without better and more numerous outlets for trainees within the National Health Service.

My thanks are due to Drs. Bunim, Daft, and Knutti, of the National Institutes of Health, for their invitation to work at the N.I.H. as a visiting scientist. They made my stay a most happy and interesting period. They, Dr. Ralph Knutti, of the extramural division, and others, spent a long time answering my rather jejune questions and decreasing somewhat my vast ignorance. They should not be held responsible for any inaccuracies or misconceptions in this document. I am indebted also to Dr. Lamont Havers, of the Arthritis and Rheumatism Foundation, and to others throughout the country too numerous to mention, for their hospitality and patience during a most interesting tour of the medical schools and universities.

Nova et Vetera

ST. PETER'S HOSPITAL FOR STONE

It must have been labour of love for Mr. Morson to edit this book* about the hospital with which he has been honourably associated for so many years. The name given to the hospital was at first peculiarly appropriate, though its scope now takes in the whole of genito-urinary surgery. There may have been some justification for the opposition to its foundation, for in 1860 Henry Thompson was working at University College Hospital and William Coulson was at St. Mary's, and indeed at first the venture was on a small, even paltry scale. Then in 1873 came a mysterious gift of ten one-thousand-pound notes by an anonymous donor (who is still unknown) and a bigger and better hospital was built. From that date its reputation rapidly grew until it became the best teaching centre of urology in this country, a position which has been recently enhanced by the foundation of the Institute of Urology. The list of famous surgeons who have been on the staff includes Reginald Harrison, Hurry (not Henry) Fenwick, Peter Freyer, Thomson-Walker, Swift Joly, and many others who have helped to make urology a more exact science. Mr. Morson pays a well-deserved tribute to Dr. Cuthbert Dukes, who put the pathological department on a sound foundation.

The nursing was at first not very good, but in 1880 Mrs. Wemyss Anderson was appointed matron and brought order out of relative chaos. It is stated that, "it is more than likely that she had had a hospital training." We can supplement this. Mrs. Anderson was for many years Lady Visitor at St. Mary's Hospital, Paddington, and in 1866, when the matron was ill, visited the hospital daily for four months to supervise the nursing. For this she received the thanks of the Board and was made an honorary governor of St. Mary's Hospital. She was therefore not without some experience. An interesting book.

ZACHARY COPE.

*St. Peter's Hospital for Stone 1860–1960. Edited by Clifford Morson, O.B.E., F.R.C.S. (Pp. 64+viii; illustrated. 21s.) Edinburgh and London: E. and S. Livingstone, Ltd. 1960.

THE BEST OF SIGERIST

Henry Sigerist was professor of the history of medicine successively at Zurich, Leipzig, and Johns Hopkins Universities. In 1947, still in middle life, he retired from his chair at Johns Hopkins to Pura, a village near Lugano in his native Switzerland. His valedictory address is included here*; and in the essay "Living under the Shadow" he records his physical handicaps, of which hypertension and associated cardiovascular disease were the most serious. Sigerist gave up an academic position that he loved, partly through ill-health but mainly to write in undisturbed tranquillity his monumental eight-volume history of medicine. Of this he completed two volumes, and then died on March 17, 1957, at the age of 65.

As Professor Fulton—alas, no longer with us—states in his foreword, while many deplore that Sigerist did not live to finish his *History*, others—including the editor of this book—consider that he achieved much more through the inspiration of his essays and miscellaneous writings, as exemplified in the collection here which was chosen by Sigerist himself. This anthology treats of medical history generally, of ancient and mediaeval medicine, baroque medicine, and medicine in an enlightened age, and of Sigerist's personal history. Each essay reveals the scholar, the depth and wide scope of his knowledge and his interpretation of a philosophy of medicine.

Even Homer sometimes nods. Sigerist, in his amusing paper on Jonas Hanway's attack on the drinking of tea (1757), is incorrect in stating that Oliver Goldsmith never graduated in medicine. The investigations of Sir William Osler and Sir Ernest Clarke† showed that he was M.B. of Dublin University, and also M.B.Oxon *ad eundem* in 1769, as Bishop Percy stated. In "An Elizabethan Poet's Contribution to Public Health: Sir John Harington and the Water Closet," Sigerist omits to mention that this useful invention was a rediscovery in point of time, for it was known to Minoan civilization. These are trivial criticisms. In this book, admirably edited and produced, we have the best of Sigerist.

ARTHUR S. MACNALTY.

*Henry E. Sigerist on the History of Medicine. Edited by Felix Marti-Ibañez, M.D. Foreword by John F. Fulton, M.D. (Pp. 313+xviii. $6.75.) New York: MD Publications, Inc. 1960.

†E. Clarke (1914). "The Medical Education and Qualifications of Oliver Goldsmith." *Proc. roy. Soc. Med.*, VII, No. 4. *Sect. Hist. of Med.*, 88.

To-day's Drugs

With the help of expert contributors we publish below notes on a selection of drugs in current use.

Penicillinase

"Neutrapen" (Burroughs Wellcome).

Penicillin is still the most extensively used antibiotic, and it is now uncommon to encounter a person who has not received it at some time. Though remarkably free from other side-effects, it does produce more severe (and occasionally fatal) anaphylactoid reactions than other antibiotics.[1] Most of these occur when the drug is given intramuscularly, especially to patients with a history of previous allergies; but they also result from oral administration,[2,3] and with the more widespread use of the latter the number of such reactions may be expected to increase. The latest figures from the Registrar-General show that in the two years 1957–8 there were eight deaths in England and Wales due to sensitivity to penicillin.[4]

Pharmacology.—Penicillinase was discovered in 1940 by E. P. Abraham and E. Chain.[5] It is produced by many strains of bacteria. The commercial product "neutrapen" is obtained from cultures of *Bacillus cereus*. By hydrolysing penicillin to penicilloic acid, which is non-antigenic, it rapidly reduces the concentration of penicillin in the blood. In removing the antigen, penicillinase has proved a valuable remedy in the treatment of penicillin reactions. It is given intramuscularly in doses of 800,000 units dissolved in 2 ml. of sterile distilled water.

Therapy.—In cases of anaphylactoid shock due to penicillin, neutrapen should be injected as soon as possible—adrenaline and other supportive measures being given coincidentally. In delayed serum-sickness-like reactions, often associated with urticaria, arthralgia, and pruritus, antihistamines or, in severe cases, corticosteroids should be given in addition. This combined therapy lessens morbidity and decreases discomfort and the likelihood of recurrence.[6]

In about 80% of cases the response to a single injection of 800,000 units of penicillinase will be completely satisfactory in 12 to 96 hours.[7] If no response occurs in that time, a second injection should be given, and should this also prove unsuccessful some other allergen should be considered to be the cause of the reaction.

Penicillinase is not an immediate panacea for all penicillin reactions: on occasions it effects relief dramatically within a few hours, but once a definitely severe inflammatory reaction has developed, even though the circulating antigen has been effectively removed or detoxified, some time may elapse before complete regression occurs. The sooner penicillinase is given after the reaction starts, the more quickly it disappears. Such regression may, of course, occur spontaneously, but as there is no way of foretelling whether this will result it is wise to administer penicillinase at the first sign of any reaction to penicillin, and it should constitute a permanent feature of a doctor's emergency kit.

Side-effects.—About one-third of the patients treated with penicillinase complain of a greater or less degree of transient pain at the site of the injection and a very few experience a mild febrile reaction lasting for a few hours.[8]

N.H.S. Basic Price.—1 vial of 800,000 units, 30s.

REFERENCES

1 Kern, R. A., and Wimberley, N. A., *Amer. J. med. Sci.*, 1953, **226**, 357.
2 Lang, L. P., and Clagett, H., *New Engl. J. Med.*, 1955, **253**, 652.
3 Peters, G. A., Henderson, L. L., and Prickman, L. E., *Proc. Mayo Clin.*, 1955, **29**, 634.
4 *The Registrar-General's Statistical Review of England and Wales for the Year 1958, Part III, Commentary*, 1960. H.M.S.O.
5 Abraham, E. P., and Chain, E., *Nature (Lond.)*, 1940, **146**, 837.
6 Becker, R. M., *Practitioner*, 1960, **184**, 447.
7 Minno, A. M., and Davis, G. M., *J. Amer. med. Ass.*, 1957, **165**, 222.
8 See *Brit. med. J.*, 1959, **2**, 232.

Correspondence

Because of heavy pressure on our space, correspondents are asked to keep their letters short.

"Celbenin"-resistant Staphylococci

SIR,—The Staphylococcus Reference Laboratory receives for phage-typing large numbers of strains of staphylococci, and it seemed that this material might usefully be examined to see whether any strains resistant to the new penicillinase-resistant penicillin (BRL 1241, "celbenin") were in circulation at about the time of introduction of the new antibiotic.

Between the beginning of October and the end of November, 1960, 5,440 strains have been tested. 4,340 of these strains were from routine material from hospitals, largely from South-eastern England; some were from other parts of the country and from abroad. Not all the 4,340 are truly independent strains. The great majority were penicillin-resistant and many were resistant to several antibiotics. The remaining 1,100 strains were isolated during October and November, 1959, from nasal swabs of healthy R.A.F. personnel.

Methods

Each strain was tested in the first place by placing a paper disk containing 10 μg. celbenin on the plate culture used in phage-typing. The celbenin was kindly supplied by Beecham Research Laboratories Ltd. Tube sensitivity-tests were carried out using twofold dilutions of the drug from 100 μg./ml. to 0.1 μg./ml. in Oxoid broth No. 1. Tubes were inoculated with 0.02 ml. of a 3-hour broth-culture of the organism and read after incubation at 37° C. for 18 hours. This test was done in duplicate using two separate colonies from a blood plate. Subsequently the test was repeated using concentrations of celbenin at 1 μg. intervals between 24 and 1 μg./ml.; all the tubes were plated to blood-agar plates for purity and phage-typing after 18 hours' incubation, and the tubes were then reincubated.

Results

Of the 5,440 strains only three showed significant resistance by the paper-disk method. All three were received from the same hospital, and I am indebted to Dr. C. Rickwood Lane for his help in supplying the information on these strains. They were of the same phage-type (7/47/53/54/75/77) and were resistant to penicillin G, streptomycin, and tetracycline. They were derived from a nephrectomy wound in patient A, an infected skin lesion in Nurse B working in the same ward, and from the nose of patient C swabbed two weeks later in the same ward. This patient C had, however, attended the hospital in July as an out-patient, when she had an eczematous lesion from which a strain of the same phage-type was recovered; she

Sensitivity to Celbenin in Tube Tests with Doubling Dilutions

Strain	Date of Isolation	Source	Site	Minimal Inhibitory Concentration of Celbenin (μg. per ml.)	
13136	2/10/60	Patient A	Nephrectomy wound	Colony a	12·5
				,, c	6·5
13137	2/10/60	Nurse B	Finger infection ..	,, a	12·5
				,, c	25·0
10395	21/7/60	Patient C	Nose	,, a	6·25
				,, b	
10396	5/7/60	,, C	Eczematous skin ..	,, a	3·125
				,, b	
14083	28/10/60	,, C	Nose	,, a	1·60
				,, b	
14668	8/11/60	,, C	,, ...	,, a	25·0
				,, b	

was admitted to another ward at that time, and discharged some weeks later. She was only admitted to the ward from which the wounds infected with the resistant strain were first detected after the nephrectomy patient was discharged and the nurse's lesion had healed.

The results of the tube sensitivity-tests on the six strains are given in the Table. Coagulase-positive staphylococci are normally sensitive to 1.25–2.5 μg./ml. celbenin.[1]

It is interesting that the four strains from the eczematous patient show different minimal inhibitory concentrations but that the two colonies tested from each culture showed the same sensitivity. This has not been explored further. Assay of residual celbenin in broth after growth of strain 13137 failed to demonstrate destruction of the antibiotic.

No direct connexion between the strain isolated from the eczematous patient in July and the two strains isolated in October could be demonstrated. Nurse B was not on duty in the out-patient department or the ward to which the patient was admitted in July, and she was not a nasal carrier at the end of October when her lesion had healed. It seems, however, very likely that the strain isolated from patient C in July was in fact the same as that isolated from patient A and nurse B in October, especially as the original patient with the infected eczema is a regular hospital attender, and this strain has been isolated from her nose three times over a three-month period and from her skin on the only occasion this was swabbed.

Celbenin had been used for one patient in this hospital. This was during October, but the patient, a diabetic with multiple boils, was treated in a side ward by a different nursing staff, and the infecting organism was a staphylococcus of phage-type 80/81. It does not seem, therefore, that the resistant strains could have arisen as a result of this therapy.

It is interesting that the celbenin-resistant strains belong to Group III phage-pattern, as it is in this group that the first staphylococci resistant to each new antibiotic have arisen. Even supposing the three strains isolated represent two naturally occurring strains, the frequency of resistant strains is only 0.036% in this series. Several other workers have failed to find resistant strains in the large number of strains tested.[2,3] Of the 4,340 strains from routine material in this series the great majority were penicillin-resistant hospital strains, and many of them were resistant to several antibiotics. The finding of these strains does not therefore detract from the very great value of celbenin, but the fact that the occasional resistant strain does exist should be borne in mind.

It is well known that patients with infected skin can be dangerous sources of infection in hospitals, and the finding of just such a patient infected with a celbenin-resistant strain in this instance adds an additional warning.—I am, etc.,

M. PATRICIA JEVONS.

Staphylococcus Reference Laboratory,
Colindale, London N.W.9.

REFERENCES

1 Rolinson, G. N., Stevens, S., Batchelor, F. R., Cameron Wood, J., and Chain, E. B., *Lancet*, 1960, 2, 564.
2 Stewart, G. T., Nixon, H. H., and Coles, H. M. T., *Brit. med. J.*, 1960, 2, 703.
3 Thompson, R. E. M., Harding, J. W., and Simon, R. D., *ibid.*, 1960, 2, 708.

SIR,—In October, 1960, we received from Dr. M. P. Jevons two single-colony isolates each of two strains of staphylococci which she had found to be resistant to "celbenin." These are the cultures referred to in her letter above and designated 13136a and c and 13137a and c. Subsequently, we also received from Dr. Jevons the original cultures 13136 and 13137 which had been sent to Colindale for phage-typing. The origin of these cultures is described in her letter.

We tested the sensitivity of these cultures to celbenin by serial dilution in agar and in nutrient broth. The broth dilutions were inoculated with one drop of an overnight broth-culture and the agar dilutions by streaking with a loopful from an overnight broth culture. The tests were incubated at 37° C. for 24 hours. Both types of tests gave the same results. With culture 13136, and also the isolates from 13136, the minimum inhibitory concentration (M.I.C.) of celbenin was 5.0 μg./ml. The normal M.I.C. for penicillin-resistant staphylococci in these tests is 2.0 μg./ml. With culture 13137, and one of the isolates from 13137, the M.I.C. was 25 μg./ml. In every case the end-point was sharp. In the broth-cultures growth was heavy up to the M.I.C. value, but with no visible growth beyond this concentration. On further incubation, however, a very different result was obtained. After 48 hours' incubation all the cultures showed heavy growth in broth culture up to and including a concentration of 250 μg./ml. Strains were isolated from this growth in 250 μg./ml. which, on subsequent testing, showed M.I.C. values of 250–500 μg./ml. after overnight incubation.

The cultures 13136 and 13137 thus appeared to be predominantly of a type not appreciably different in sensitivity to celbenin from other penicillin-resistant staphylococci, but in addition there appeared to be a very small proportion which were highly resistant. Plating out large numbers of cells of 13136 and 13137 on agar-containing doubling dilutions of celbenin showed that after incubation overnight at 37° C. only one in approximately 10^7 of the population grew at 12.5 μg./ml. and only one in approximately 10^8 grew at a concentration of 250 μg./ml.

The resistant type isolated from broth cultures containing 250 μg./ml. of celbenin grew well on 7.5% salt agar, gave acid production with mannitol and liquefaction of gelatin, and was coagulase-positive. The culture was also penicillinase-producing, penicillin-resistant, and resistant also to streptomycin and tetracycline, as was the rest of the culture. Phage-typing, which was kindly carried out by Dr. Jevons, showed this resistant strain to be of the same phage-type as the rest of the culture. A pure culture of the resistant strain grew up readily overnight in broth in concentrations of celbenin up to 250 μg./ml. Assay of the celbenin-content of these broths from 1.0–250 μg./ml. after 24 hours' incubation showed no detectable destruction of celbenin compared with uninoculated broths incubated in the same way. The resistance of this culture is therefore not due to celbenin-destruction by a "celbeninase."

Staphylococci resistant to celbenin can, of course, be obtained quite readily *in vitro* by repeated subculture in the presence of the compound. Whether this is of any significance from the clinical point of view, however, is another matter. Resistance of this type also develops very readily to penicillin G, but cultures of this type are never encountered clinically, and, so far, strains resistant to celbenin have not been isolated from patients following treatment with this antibiotic. When celbenin was marketed in September, 1960, no strains of penicillin-resistant *Staphylococcus aureus* had been found which were resistant to celbenin. Since that time very large numbers of strains have been screened in different laboratories in this country and elsewhere. However, the only strains so far reported to be resistant to celbenin are those described in this letter and the accompanying letters. From the total number of strains examined by Dr. Jevons and those covered in the published literature[1–3] the incidence of celbenin-resistant strains of *Staphylococcus aureus* appears to be less than one in 5,000 of the strains encountered in hospitals

to-day. Resistant strains of the type described in this letter are remarkable more for their infrequency than for their existence.—I am, etc.,

Beecham Research Laboratories Ltd., Betchworth, Surrey. G. N. ROLINSON.

REFERENCES

1 Elek, S. D., and Fleming, P. C., *Lancet*, 1960, 2, 569.
2 Knox, R., *Brit. med. J.*, 1960, 2, 690.
3 Rolinson, G. N., Stevens, S., Batchelor, F. R., Cameron-Wood, J., and Chain, E. B., *Lancet*, 1960, 2, 564.
4 Stewart, G. T., Harrison, P. M., and Holt, R. J., *Brit. med. J.*, 1960, 2, 694.
5 Thompson, R. E. M., Harding, J. W., and Simon, R. D., ibid., 1960, 2, 708.

SIR,—The new penicillin, BRL 1241 ("celbenin"), has already proved its worth in the treatment of penicillin-resistant staphylococcal infections. But it is now clear that, as judged by laboratory sensitivity tests, there are at least two types of resistance to celbenin in staphylococci. In several laboratories resistant strains have been artificially produced by different methods of subculture in celbenin-containing media.[1-3] We ourselves have now produced variants resistant to at least 500 μg./ml. of the drug from a strain of *Staph. pyogenes* (E3) initially sensitive to 2–5 μg./ml.[2] The second type of resistance, which may be more serious, is reported in the accompanying letter (p. 124) by Dr. Patricia Jevons from the Staphylococcus Reference Laboratory, Colindale. She has investigated the celbenin-sensitivity of several thousand strains of *Staphylococcus pyogenes* isolated mainly from hospital sources from different parts of the country. One small group of strains which were all of the same phage-type and were isolated from three persons in one hospital showed increased resistance ranging from 6 to 25 μg./ml. as compared with the normal range of 2 to 5 μg./ml.

The terms sensitive and resistant can be misleading, especially when only simple sensitivity tests are done, using serial drug-dilutions with a large inoculum of organisms. Often, more information is required about the distribution of resistance within bacterial populations. This can be obtained only by more elaborate experiments in which different inocula are tested against different concentrations of the drug.

We have investigated a number of strains of *Staph. pyogenes* in this way. Among the strains used have been the penicillinase-producing strain E3 from a patient already mentioned and a laboratory-trained variant of this made resistant by repeated subculture in celbenin to 500 μg./ml. of the drug (E3/500), some naturally occurring celbenin-resistant strains kindly provided by Dr. Patricia Jevons (13136, 13137, 14083, 10395) and some variants of 13137 made resistant in this laboratory by subculture in celbenin to 50, 400, and 1,000 μg./ml. of the drug (13137/50, 13137/400, and 13137/1000). With each strain serial tenfold dilutions of broth cultures were inoculated on to agar plates containing different concentrations of celbenin and on to plain nutrient agar. Thus the number of organisms inoculated was known and a rough estimate could be made of the proportion surviving in different concentrations of the drug.

The results may be briefly summarized:

1. With the E3 strain all the inoculated cells survived in 3 μg./ml. of celbenin but none in 6 μg./ml. even when 10^6 cells were inoculated. Strain 13137 from Colindale was quite different. All the cells inoculated survived in 3 μg./ml., about 1 in 10^6 cells survived in 12 μg./ml., while only 1 in 10^7 survived in 100 μg./ml. Two of the other Colindale strains, 13136 and 10395, behaved similarly, but strain 14083, although from the same patient as 10395, was more like a normally sensitive strain.

2. The laboratory-trained resistant variants, E3/500 and 13137/1000, were interesting. When first isolated both strains grew much more slowly even on drug-free medium than their parent strains, but the 13137/1000 variant from the naturally resistant strain 13137 quickly recovered the ability to grow normally on nutrient agar, whereas the E3/500 variant from the naturally sensitive strain E3 still gives poor growth. With both strains, however, all the cells inoculated grow up to high concentrations of celbenin on longer incubation.

3. There has been no evidence so far that any of these strains can destroy celbenin. This has been investigated both by microbiological and chemical assay methods.

These facts are clearly important, but must be viewed in proper perspective. On the one hand, it would be foolish to ignore the facts (1) that strains naturally resistant to celbenin actually existed before the drug was used, and (2) that cultures of *Staph. pyogenes* can be "trained" artificially in the laboratory to high levels of resistance. On the other hand, it should be emphasized (1) that mutants resistant to celbenin were bound to be detected if they were looked for thoroughly enough, and Professor R. E. O. Williams, who with Dr. Jevons initiated this investigation at Colindale, should be congratulated on seizing the opportunity for this presented by the existence of the staphylococcus reference laboratory, (2) that it is the rarity of this resistance rather than its frequency which is remarkable, and (3) that so far there have been no reports of failure due to the development of celbenin-resistant staphylococci in patients treated with it.

We must, of course, be always on the look-out for resistant strains. We must avoid indiscriminate use of the drug which is only likely to increase the chances of such strains spreading. But these warnings should not make us afraid to use the drug where it is properly indicated and to take full advantage of its remarkably effective action against penicillin-resistant staphylococci.—I am, etc.,

Department of Bacteriology, Guy's Hospital Medical School, London Bridge, S.E.1. R. KNOX.

REFERENCES

1 Rolinson, G. N., Stevens, S., Batchelor, F. R., Cameron-Wood, J., and Chain, E. B., *Lancet*, 1960, 2, 564.
2 Knox, R., *Brit. med. J.*, 1960, 2, 690.
3 Barber, Mary, ibid., 1960, 2, 939.

Aetiology of Coronary Disease

SIR,—In a recent paper (November 5, 1960, p. 1329) concerned with the pathogenesis of coronary artery disease, Sir Howard Florey mentioned that some investigators consider the protein content of the diet to be of great importance (possibly as important as the lipid content) in controlling serum lipid levels. I think it is also of interest that over 30 years ago Mills and Necheles[1-4] observed increased coagulability of the blood *in vitro* as well as acceleration of platelet aggregation and disintegration following the ingestion of protein; on the other hand, no such changes were seen after either fat or carbohydrate had been given. Furthermore, it is generally recognized that communities showing the lowest incidence of ischaemic heart disease subsist on diets which contain relatively small amounts of protein (especially animal protein) as well as of fat.[5] Some of us have the impression, too, that

gross atheroma is rare in patients with chronic alcoholism, a condition commonly associated with severe protein deficiency. It would seem, therefore, that the degree of protein consumption is yet another factor which will require investigation during the course of further research designed to establish the aetiology of coronary artery disease.—I am, etc.,

Medical Research Laboratories, Charing Cross Hospital, London W.C.2. M. A. PEYMAN.

REFERENCES

1 Mills, C. A., and Necheles, H., *Proc. Soc. exp. Biol. (N.Y.)*, 1927, **25**, 195.
2 —— —— *Chin. J. Physiol.*, 1928, **2**, 19.
3 Necheles, H., and Mills, C. A., ibid., 1928, **2**, 25.
4 Mills, C. A., Necheles, H., and Mao-Keng Chu, ibid., 1928, **2**, 219.
5 Ahrens, E. H., jun., *Amer. J. Med.*, 1957, **23**, 928.

Post-mortem Serum Cholesterol

SIR,—Dr. J. N. Glanville's data (December 24, 1960, p. 1852) are a useful contribution in a field that has been little explored. In fact, its contours are extremely complex. In 1936 Lande and Sperry,[1] at Schonheimer's suggestion, made successful cholesterol analyses on cadaver sera, and Faber[2] considered that any differences encountered in serial estimations were within the limits of experimental error. More recently Paterson and Dyer[3] have compared ante- and post-mortem blood-cholesterol levels in a closed population and have concluded that they were comparable provided death was sudden.

I have been collecting data from cadaver sera for some years now, and I believe that all these authors have in fact missed a small autolytic change. Many serum constituents, particularly enzymes, increase very rapidly in the serum for a few hours after death, then slowly for 48 hours before falling off again. In very old bodies there is often a further final rise.[4] These changes are much less striking in non-protein substances and in them the initial sharp rise is not seen. The effect of this rather complex change is that in most cases in which analysis is likely to be contemplated—that is, those of simpler constituents on sera obtained within two days of death—a direct linear increase with time can be expected. My data are based on analyses now of nearly 1,000 cadaver sera, and the curves have been constructed by simply relating time after death to result of analysis. The values obtained in several hundred cholesterol analyses give means in successive 12-hour periods of 195, 207, 213, 232, followed by a fall to 200 in the 49- to 60-hour period. There is thus an hourly increment of about 0.5 mg. per 100 ml. The conventional Bloor method was used.

Such a correction does indeed give discrepancies well within the experimental limits but quite large enough to have a 20 : 1 significance in large groups with differing mean times after death. I have, however, quite insufficient data on pairs of ante- and post-mortem analyses to plot the point corresponding to the 12 hours preceding death. If Dr. Glanville would do this, the information would be most valuable and would, I think, be unique.—I am, etc.,

East Ham Memorial Hospital, London E.7. J. B. ENTICKNAP.

REFERENCES

1 Sperry, W. M., in *Chemistry of Lipids as Related to Atherosclerosis*, 1958, ed. I. H. Page. Thomas, Springfield, Illinois.
2 Faber, M., *Acta med. scand.*, 1946, **125**, 418.
3 Paterson, J. C., and Dyer, L., *Circulation*, 1959, **20**, 989.
4 Enticknap, J. B., *J. forensic Med.*, 1960, **7**, 135.

Antibody to Penicillin

SIR,—We read with great interest your leading article on this matter (August 6, p. 444), as it seems you were not aware that the findings of Ley *et al.*[1] have been confirmed and extended by us in a Spanish paper with an English summary.[2] The work of Watson *et al.*[3 4] was published after this. We found antibodies to penicillin-treated red cells in the sera of four out of nine patients with penicillin shock, and Epp[5] reported similar results. However, in such haemagglutinating sera we did not detect precipitins, and tests of passive transfer of sensitivity with these sera were negative. Thus, your conclusion that "the basis of sensitivity to penicillin must be sought elsewhere" and not in the haemagglutinin has been anticipated. There is yet another point. What seems to be antibody to penicillin may act in fact on an accompanying substance.—We are, etc.,

Faculdade de Medicina, São Paulo, Brazil. F. OTTENSOOSER. E. MENDES.

REFERENCES

1 Ley, A. B., *et al.*, *Science*, 1958, **127**, 1118.
2 Ottensooser, F., and Mendes, E., *Sangre*, 1958, **3**, 417.
3 Watson, K. C., Joubert, S. M., and Bennett, M. A. E., *Nature (Lond.)*, 1959, **183**, 468.
4 —— *J. Immunology*, 1960, **3**, 1.
5 Epp, M., *Science*, 1959, **130**, 1472.

Arteritis

SIR,—In connexion with the article by Drs. J. W. Paulley and J. P. Hughes (November 26, p. 1562), the possibility of an immunological phenomenon being concerned with the causation of temporal arteritis was mentioned in correspondence by Dr. G. D. Kersley (December 31, p. 1953). Together with my laboratory colleagues I have been working on these lines for the past two years. Since much of the inflammatory activity appears histologically to be centred around damaged elastic tissue, we have worked principally with elastin and its soluble derivatives. Experimental work, to be published elsewhere, has not so far afforded any evidence for the hypothesis that temporal arteritis is a disease associated with an auto-immune reaction involving elastin or its soluble derivatives.—I am, etc.,

The Royal Infirmary, Sheffield. G. V. BALMFORTH.

Pathology of Chronic Bronchitis

SIR,—Your annotation (December 31, 1960, p. 1946) on the pathology of chronic bronchitis raises several interesting points. The histological changes in chronic bronchitis consist not only in the increase in size and number of deep mucous glands but in the more or less complete loss of the normal serous glands and of the demilunes of serous cells normally found in some mucous glands. Whether the serous cells atrophy or are converted to mucus-secreting cells is unknown.

In a recent study of bronchial biopsies from patients with chronic bronchitis and asthma, Dr. Michaels and I found[1] that the mucoid change was almost entirely confined to patients with chronic bronchitis—that is, those who had had persistent or recurrent cough and sputum for at least two years. Cases of pure asthma—that is, with no coincident or superimposed chronic bronchitis—with few exceptions had the normal predominantly serous pattern of deep glands even after many years. It is interesting that in the series of deaths in status asthmaticus recorded by Houston, De Navasquez, and Trounce[2] the bronchi were

completely obstructed by mucus, yet the deep glands were histologically normal.

Within the bronchitic group of biopsies, the degree of mucous change was not related to the use of tobacco or the presence of infection but depended on the duration of the disease. Anything more than slight change was only found in bronchitics with at least ten years' history, while the most severe changes occurred in patients with over twenty years' history.

Goblet cells are more easily studied in biopsy that in necropsy specimens. In the series referred to above, goblet cell hyperplasia was equally common in cases of bronchitis, asthma, and bronchitis with asthma. It bore no relation to the degree of mucoid change in the deep glands but was significantly more frequent where there was infection with *H. influenzae*.—I am, etc.,

St. Mary's Hospital Medical School, London W.2. A. A. GLYNN.

REFERENCES

1 Glynn, A. A., and Michaels, L., *Thorax*, 1960, **15**, 142.
2 Houston, J. C., De Navasquez, S., and Trounce, J. R., ibid., 1953, **8**, 207.

Megaloblastic Madness

SIR,—We would like to congratulate Dr. A. D. M. Smith (December 24, 1960, p. 1840) on his important paper. Dr. Smith refers to the results of our study of 14 male patients with tobacco amblyopia seen at the Bristol Eye Hospital which showed that an essential feature was a low vitamin-B_{12} concentration in the serum.[1] However, his statement that "unfortunately bone-marrow studies were not performed in this series" is not strictly accurate. It was, in fact, decided that biopsy of the sternal marrow should be undertaken in every case of tobacco amblyopia with histamine-fast achlorhydria and evidence of neurological involvement, irrespective of whether or not anaemia was present. Using this method of selection we found two patients had a megaloblastic bone-marrow and one patient a normoblastic marrow.

We certainly did not expect that low or very low serum vitamin-B_{12} levels would also be found in patients with free acid on gastric analysis, and in this clinical trial we did not feel justified in withholding treatment with cyanocobalamin till the results of microbiological assay were available in view of the frequency of severe and progressive deterioration of vision. Now, being wise after the event, we entirely agree with Dr. Smith that it would have been of considerable interest to know if biopsy of the marrow showed normoblastic or megaloblastic erythropoiesis in our remaining cases.

In this connexion, we would like to refer briefly to one of our cases included in our series. The presentation of tobacco amblyopia and mental changes, consisting of acute depression, irritability, lack of concentration, and failing memory, in a non-anaemic man, aged 52, is of particular interest. Although free acid was present in the gastric juice, the serum vitamin-B_{12} level was exceptionally low at 15 $\mu\mu$g./ml. We therefore suggested that in any case of unexplained peripheral neuropathy, myelopathy, or encephalopathy the concentration of vitamin B_{12} in the serum should be measured, *even if histamine-fast achlorhydria is not present*. The interesting findings of Dr. Smith add further support to this view.—We are, etc.,

Princess Margaret Hospital, Swindon, Wiltshire. A. G. FREEMAN.
Institute of Ophthalmology, London W.C.1. J. M. HEATON.

REFERENCE

1 Heaton, J. M., McCormick, A. J. A., and Freeman, A. G., *Lancet*, 1958, **2**, 286.

SIR,—May I plead that your contributors cease using the word "madness" when describing a new, or apparently new, diagnostic category? Apart from the fact that this word carries prejudices in both medical and lay circles, it can mislead: madness implies a pretty severe form of mental disorder whereas, as Dr. A. D. M. Smith points out at the beginning of his excellent paper (December 24, 1960, p. 1840), the mental symptoms in "megaloblastic madness" vary from the mildest to the most severe; and a mild neurotic reaction or mood swing is not "madness."

Nearly thirty years ago, when I reported a relevant case,[1] I was content to use the phrase "mental disease." It would be interesting to know whether there is a valid medical or social reason for the increasing use of the word "madness." If one of your readers can supply this, I shall resign myself to a series of articles, not only on "megaloblastic madness," but also on "myxoedematous madness," "diabetic madness," "syphilitic madness," "influenzal madness," and so forth.—I am, etc.,

Park Prewett Hospital, Basingstoke. I. ATKIN.

REFERENCE

1 Atkin, I., *Lancet*, 1932, **2**, 569.

Familial Pseudocholinesterase Deficiency

SIR,—Dr. F. D. Adrianvala (December 31, 1960, p. 1955) finds that none of the members of the family of a case of suxamethonium apnoea with low pseudocholinesterase was similarly affected. He is correct in concluding that "these results lend no support to the suggestion of any genetic behaviour on the part of pseudocholinesterase deficiency." We can furnish Dr. Adrianvala with hundreds of examples of patients with low pseudocholinesterase level where there is no evidence of inheritance, but equally also with dozens where family study has borne out a "genetic behaviour on the part of pseudocholinesterase deficiency." When the genetic deficiency was first postulated[1] it was made clear that pseudocholinesterase is low in the majority of cases because of liver disease, extreme malnutrition, etc., but that there had been instances where the clinical findings did not correlate with the laboratory results. When the families of such individuals with low pseudocholinesterase (usually discovered because of their sensitivity to suxamethonium) were investigated the picture of a familial deficiency emerged.[2–5]

Fortunately it is now possible to determine *in vitro* whether a low pseudocholinesterase level is of the inherited or the acquired type. Kalow and his collaborators found in Canada[4–5] that, in the familial type, normal enzyme is replaced by another which is not only less active but also shows a diminished sensitivity to inhibition by dibucaine (cinchocaine). The percentage inhibition is constant for any one individual and is independent of variations in enzyme level. Kalow has devised a test system in which plasmas from normal homozygotes lose 80% of their activity in the presence of dibucaine, and those of abnormal homozygotes are inhibited to only about 16%. Furthermore, whereas the range of pseudocholinesterase levels of heterozygotes overlaps at both ends with those found in abnormal and normal homozygotes, there is no such overlap in the range of pseudocholinesterase inhibition by dibucaine, which for heterozygotes lies midway between the 80% and 16% inhibition of normal and abnormal homozygotes respectively at about 60%.

In collaboration with Professor H. Harris and Dr. Mary Whittaker we have recently compared the pseudocholinesterase activity and the sensitivity towards dibucaine in

eleven of our families—69 individuals in all.[9] Kalow's observations were largely confirmed, and at this hospital we now determine as a matter of routine the "dibucaine number" of every plasma with a pseudocholinesterase level below 30 Warburg units (normal 65–120). This decides whether the low result indicates loss of liver function or is due to an inherited defect. For example, a level of 29 units indicates in the normal a considerable loss of active liver tissue, and in the heterozygote a much milder condition.

It is hoped that Dr. Adrianvala's observation and conclusion will not be interpreted as contradicting the article and letter by Dr. L. Kaufman and his colleagues.[5 10] Examination of families of patients who exhibited suxamethonium apnoea with pseudocholinesterase deficiency is not merely an academic exercise but can be of great importance to hitherto undiscovered homozygotes. They are not only hypersensitive to suxamethonium but also to pseudocholinesterase inhibitors used in agriculture, in the car and aircraft industry, as well as in many other fields of twentieth-century endeavour.—We are, etc.,

H. LEHMANN.
ELSIE SILK.

St. Bartholomew's Hospital,
London E.C.1.

REFERENCES

1 Lehmann, H., and Ryan, E., *Lancet*, 1956, **2**, 124.
2 Forbat, A., Lehmann, H., and Silk, E., ibid., 1953, **2**, 1067.
3 Lehmann, H., Patston, V., and Ryan, E., *J. clin. Path.*, 1958, **11**, 554.
4 —— and Simmons, P. H., *Lancet*, 1958, **2**, 981.
5 Kaufman, L., Lehmann, H., and Silk, E., *Brit. med. J.*, 1960, **1**, 166
6 Kalow, W., and Staron, N., *Canad. J. Biochem. Physiol.*, 1957, **35**, 1305.
7 —— and Gunn, D. R., *Ann. hum. Gen.*, 1959, **23**, 239.
8 —— and Davies, R. O., *Biochem. Pharmac.*, 1958, **1**, 183.
9 Harris, H., Whittaker, M., Lehmann, H., and Silk, E., *Acta genet.*, 1960, **10**, 1.
10 Kaufman, L., Lehmann, H., and Silk, E., *Brit. med. J.*, 1960, **2**, 535.

Suxamethonium and Cardiac Rhythm

SIR,—May I add a few words to the paper of Drs. K. G. Lupprian and H. C. Churchill-Davidson (December 17, p. 1774) on suxamethonium-induced disturbances of cardiac action? About a year ago, whilst abroad, I also started some work on this subject, again stimulated by Bullough's original letter.[1] In my trial I attempted (*a*) to confirm that suxamethonium could cause cardiac disturbance when given intermittently, and (*b*) to assess the value of the parasympatholytic agents used in premedication. The patients were all fit young people undergoing minor surgical or gynaecological procedures and were divided into three groups:

Group	*Premedication*	*No. of Cases*
1	Pethidine and atropine	6
2	Pethidine and promethazine	3
3	Papaveretum and hyoscine	1

Induction was with thiopentone and maintenance with nitrous oxide (6 litres) and oxygen (2 litres) using a Draeger circle absorber with a facemask. Respiration was controlled manually during apnoea with some degree of hyperventilation. Lead II electrocardiograms were recorded after induction to obtain a normal baseline and throughout the injection of suxamethonium. All patients had an indwelling intravenous needle *in situ* before recording commenced.

Those patients in Group 1 showed no disturbance of cardiac rate or rhythm at all after multiple injections of suxamethonium. In all cases the initial dose was 50 mg. and subsequent doses (given as signs of respiration returned) were of 20 mg. Various dilutions (50 mg. per ml. and 10 mg. per ml.) and different rates of injection were employed without any recordable difference.

In Group 2, however, there were definite changes. Two cases showed simple sinus bradycardia after the second dose of suxamethonium without other abnormality. Atropine 1 mg. intravenously produced immediate sinus tachycardia, and no further changes occurred with subsequent doses of suxamethonium. The third patient in this group, a woman undergoing dilatation and curettage, received an initial dose of suxamethonium of 50 mg. and a second dose of 20 mg. After 16 seconds there was a progressive depression in the height of the P-wave (Fig. 1) and a simultaneous bradycardia (fall in rate from 120/min. to 34/min.). The P-wave ultimately disappeared. A nodal rhythm occurred and intravenous atropine, 1 mg., caused immediate reversion to sinus rhythm.

Only one patient was observed in Group 3. He was a fit young man for interval appendicectomy and had, owing to operating delays, received his premedication 1½ hours before reaching the theatre. Recording was commenced and he received 50 mg. and 20 mg. of suxamethonium. 25 seconds after the second dose a sudden bradycardia occurred and his heart stopped (Fig. 2). Artificial respiration with pure oxygen under increased pressure was started immediately and 1 mg. of atropine injected (washed in with water and the arm elevated and massaged centrally). After 25 seconds' asystole, vagal escape occurred and normal sinus rhythm returned. At this time the patient was just beginning to show a greyish facial pallor, but unfortunately the pupils were not examined. The colour returned immediately normal rhythm was re-established and the patient gave no further cause for alarm. His recovery from the anaesthetic was completely normal.

Thus my findings differ from Drs. Lupprian and Churchill-Davidson in that (*a*) the effect of suxa-

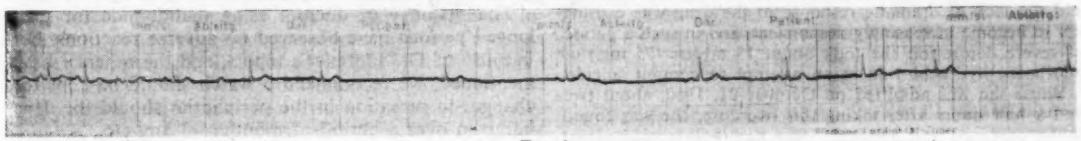


FIG. 1

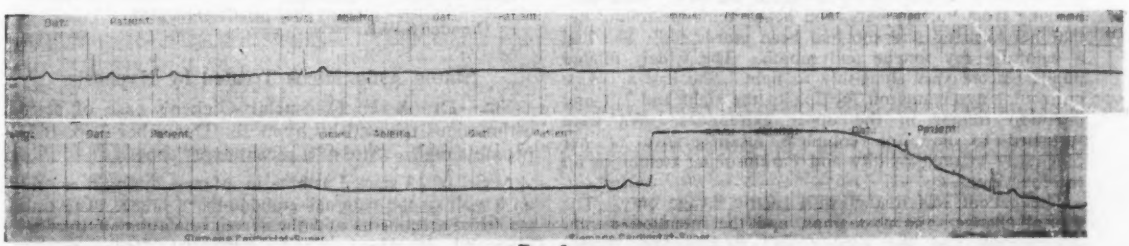


FIG. 2

methonium can occur with smaller initial and second doses than they found, and (*b*) the period of asystole can be prolonged beyond 7 seconds. Bullough originally reported arrest of "up to 16 seconds or even more."

The progressive depression of the P-wave suggested that the site of action might be direct on the atrial myocardium, and this, in conjunction with the work of McKendrick and Godfrey[2] on biochemical initiation of the cardiac impulse, led to some work on isolated rabbit atria *in vitro*. Unfortunately, this work was interrupted by my return to England and was never completed. No effect had been demonstrated. However, as all the apparatus was home-made and definitely makeshift, this method may yet provide further information. This work also suggests that intermittent suxamethonium may be more dangerous in patients on "serpasil"—with depleted tissue sympathomimetics—or any form of relatively increased vagal tone.

I now give intravenous atropine routinely to all patients requiring more than one dose of suxamethonium.—I am, etc.,

University College Hospital, London W.C.1. B. FOSTER.

REFERENCES

1 Bullough, J., *Brit. med. J.*, 1959, **1**, 786.
2 McKendrick, C. S., and Godfrey, A. M., *Lancet*, 1959, **2**, 482.

Benzhexol Hydrochloride Poisoning

SIR,—Benzhexol hydrochloride has been used in this country for the treatment of Parkinsonism since 1949. It reduces the rigidity and tremors, and controls sialorrhoea. Cunningham *et al.*[1] found that its antispasmodic effects on isolated intestinal muscle were half as powerful as that of atropine. They found that in small doses the parasympatholytic effects were accompanied by mild depression of the central nervous system, and in larger doses by excitement. Although the side-effects of benzhexol hydrochloride used in the treatment of Parkinsonism have been recognized for a number of years, no case of acute poisoning with this drug has been recorded in recent medical literature. I would like to describe such a case.

A 47-year-old married woman had encephalitis lethargica in 1924 at the age of 11, and developed Parkinsonism at the age of 32, and was regularly attending the out-patient department of this hospital. She was noted to have a typical Parkinsonian coarse tremor, cog-wheel type of rigidity of all limbs, and had been very troubled by oculogyric crises occurring about once weekly. The patient usually took about 10 mg. of benzhexol hydrochloride daily in divided doses. The insidious progression of the disease and the lack of dramatic response to the drug was causing her to become increasingly despondent, and in such a period of severe depression she took about 15 tablets (75 mg.) of benzhexol hydrochloride in an attempt to commit suicide.

When she was admitted on October 21, 1960, about two and a half hours after taking this overdose, she was found to be confused and agitated. She had well-formed visual and auditory hallucinations in which she saw "dead men hanging from curtain bars, and heard someone telling her that her husband and son had been murdered." She had a painfully dry tongue and mouth. The widely dilated pupils reacted very sluggishly to light. She had a coarse horizontal nystagmus on looking to the right and left and intention tremor in the upper extremities. We were surprised to find the complete disappearance of her previously marked rigidity and Parkinsonian tremor in all the four limbs.

The patient was treated with gastric lavage only. The mental changes, the nystagmus, and the intention tremor disappeared, and the rigidity and Parkinsonian tremor reappeared 24 hours after admission to the hospital. On complete recovery the patient was found to be a sensible person and had no obvious psychotic tendencies.

This case shows that large doses of benzhexol hydrochloride can cause acute psychosis. Serious reactions first reported in four cases by Corbin[2] were acute mental confusion, extreme agitation, and dizziness. Porteous and Ross later[3] described similar psychotic symptoms in their article on mental symptoms following the use of benzhexol hydrochloride in Parkinsonism. The patient's slurred speech, nystagmus, and intention tremor point to cerebellar disturbance, and this has not previously been noted with benzhexol hydrochloride. The other notable feature in this case was the complete temporary disappearance of extrapyramidal tremor and rigidity. It is interesting that, apart from cerebellar signs, similar toxic effects are encountered with atropine overdose.

I wish to thank Dr. D. R. Humphreys, consultant physician, United Birmingham Hospitals, for permission to report this case and also for his helpful criticism.

—I am, etc.,

Birmingham General Hospital, Birmingham. S. P. SINGH.

REFERENCES

1 Cunningham, R. W., *et al.*, *J. Pharmacol. exp. Ther.*, 1949, **96**, 151.
2 Corbin, K. B., *J. Amer. med. Ass.*, 1949, **141**, 377.
3 Porteous, H. B., and Ross, D. N., *Brit. med. J.*, 1956, **2**, 138.

Is Thalidomide to Blame?

SIR,—In view of Dr. A. Leslie Florence's letter (December 31, p. 1954) reporting a possible toxic hazard with the sedative/hypnotic drug thalidomide ("distaval"), I feel it is important to record here our present information on this aspect gleaned from four years' clinical investigations.

Until recently both animal experimental work and clinical studies had not revealed any significant toxic hazard from thalidomide, but early in 1960 isolated reports were sent to me from various parts of the country describing symptoms and signs suggestive of peripheral neuritis occurring in patients receiving thalidomide regularly for periods of six months or more. In some of these cases, because of either inadequate data or the simultaneous use of other drugs, it was impossible to say whether thalidomide was responsible. From others, however, we felt satisfied peripheral neuritis could be a toxic hazard, albeit a rare one, and since August of last year information about this has been included in literature supplied with the drug.

The majority of doctors using thalidomide for prolonged periods have observed no adverse reactions, but because of Dr. Florence's report, and the others I have mentioned, we recommend a watch should be kept for changes in sensation in the peripheries should the drug be given over a period of months.—I am, etc.,

Clinical Research Department, The Distillers Company (Biochemicals) Limited, London S.W.1. DENIS BURLEY.

Status Asthmaticus Treated by Hypnosis

SIR,—Dr. A. H. C. Sinclair-Gieben's case of status asthmaticus relieved by hypnosis (December 3, p. 1651) prompts me to write of a recent experience.

A girl of 13 started asthma in infancy, during a car ride on a visit to the paternal grandmother's home. The usual medicinal treatments and the recommendation of tonsillectomy and adenoidectomy and a residential school were given

and effected by a children's hospital. For two years, away from home, the child was well. Just one year ago, without prior consultation or advice, the child was brought home. She attended school regularly and was surprisingly well. At Whitsun the parents decided to revisit the grandmother's home, and arrived back with the patient in status asthmaticus. Her attack was relieved by hypnosis and she was seen for three more sessions, taught auto-hypnosis, and her chest was clear and she appeared well. On June 30 a night call found the child unconscious, sprawled across the father's lap, frothing at the mouth, cyanosed, with carpo-pedal spasm, not rousable, with a positive Babinski, and barely audible breathing.

I was sufficiently frightened to rush her to hospital in my car, the father meantime attempting artificial respiration. Thanks to the excellent efforts of the R.M.O. with oxygen and intravenous calcium gluconate and later intramuscular paraldehyde she recovered and was admitted. She was observed, on no treatment, and there was noted to be a definite relationship between her attacks of bronchospasm and the ward rounds and the visits of her parents. The paediatrician advised the parents as to their future conduct in warding off attacks. The excellent advice was given me: 'It is felt that the less regular medication she has the better, and the more activities and interests she develops outside the home the more independent she will become." How certainly true and how impossible for this immature child. For, as in every case of asthma, the child is "the presenting symptom of the mother."[1]

During the child's absence at residential school, the mother became a constant attender at surgery with long-standing erythrocyanosis frigida crurum puellarum, varicosities, indigestion, amenorrhoea, thyrotoxicosis, and became an in-patient for a duodenal ulcer. It was because of this that the parents decided to bring the child home. Efforts on my part to discuss her emotional life with the mother were frustrated, and explanation of the unconscious motivation of her own and the child's illnesses never allowed.

Dr. Sinclair-Gieben too ignores the unconscious with his statement "that in status asthmaticus the distress is often out of proportion to the actual bronchospasm present, and in many cases it is probable that death would not occur if the patient kept his head."

Emotions are expressed through changes in the musculature of the body, the face, chest wall, spinal column, shoulder, diaphragm, and viscera. A connexion exists between normal thought processes and muscular activity which leads to increased muscle tension. Minor deviations of mental attitudes not considered to be illness manifest themselves in characteristic posture and movement, involving all the musculature of respiration. Respiration and movement are closely intertwined; respiratory symptoms may well be part of psychomotor impulses. The Greeks thought of mental illness in terms of the diaphragm, the seat of emotions and life, and schizophrenia was due to tensions created in the diaphragm. Hippocrates said the asthmatic must guard against anger, and Willis in 1679 thought that violent action of the body or mind led to asthma attacks. Asthmatic children tend to be friendly yet aloof, finding it difficult to show their feelings. Their mothers are colder, more brittle in a controlled panic state when the doctor comes to see the child in an attack. In every-day language we ask a stingy person to cough up. The miser wheezes asthmatically counting his ill-gotten and retained gains. Even a slight loss will produce distress, fear, and anger. The asthmatic reverses the situation, referring the whole of his emotional distress to the retention of his sputum and inability to utilize his out-giving muscles of respiration. To break the asthmatic's automatic pattern of behaviour and reaction hypnosis is useless without psychotherapy, but, with it, is the treatment of choice.—I am, etc.,

Sidcup, Kent. L. A. NICHOLS.

REFERENCE

[1] Balint, M., *The Doctor, His Patient and the Illness*, 1957. Pitman Medical Publishing Co., London.

SIR,—It was interesting to read Dr. A. H. C. Sinclair-Gieben's article on the "Treatment of Status Asthmaticus by Hypnosis" (December 3, 1960, p. 1651) and Dr. Alan Akeroyd's remarks (December 31, p. 1953) appertaining to it. To those of us who employ hypnotic treatment daily similar cures are not uncommon, and the relief obtained by means of hypnosis, when all other known remedies have failed, is dramatic.

An interesting lesson can, indeed, be learnt from this case. Dr. Akeroyd stresses the "importance of ascertaining a history of [the] deep-seated dynamics." Nobody, I think, would question this, but this can only be effected when patients are sent for treatment early—that is, when once the diagnosis of asthma has been established. When confronted with a patient in status asthmaticus there is no time to delve into deep-seated history, nor is the patient in any condition to be questioned. When death lurks around the corner, relief must be obtained immediately. Without question it is essential to deal with these "deep-seated dynamics" in a future quiescent period.

Surely the causes of all symptoms whether treated by drugs or hypnosis should be investigated prior to commencement of treatment. The influence of psyche over soma is now undisputed, but how many medical men can honestly state that in every case of insomnia they have investigated the basic cause before dispensing barbiturates, etc., or that they have delved into the hidden mysteries of a skin disease before prescribing cortisone, etc., and after all "the skin is the mirror of the soul." The danger, if there is any danger, is just as great in direct symptom removal by drugs as by hypnosis. I would state that in my experience it is by no means easy to induce any patient, even in the deepest stages of hypnosis, to part with a symptom against his basic will. Therefore, I must differ from Dr. Akeroyd's statement: "When the attack was cured he unconsciously realized that this way of escape had been removed, and so three days later he dies of acute heart failure."—I am, etc.,

London W.1. J. R. ROBSON.

Anaesthetizing the Nose

SIR,—I think it would only be fair to point out to your readers that the modification of Moffett's excellent method of producing local anaesthesia in the nose by postural instillation, described by Dr. R. I. Bodman and Mr. F. Boyes-Korkis (December 31, p. 1956), was published in the *Lancet*[1] by Dr. E. S. Curtiss.

This method has been extensively used by me and to my knowledge by many of my colleagues since Curtiss described it eight years ago. In addition to producing efficient and virtually safe and foolproof local anaesthesia, the same technique is most valuable, using vasoconstrictors alone, as a preliminary to nasal operations under general anaesthesia.

Of the efficacy of the original Moffett method in producing perfect anaesthesia I can speak from personal experience, and the reports of many patients confirm

the similar efficiency of the modification by Curtiss. I am glad to see the publication of additional support for the method.—I am, etc.,

The Queen Elizabeth Hospital, Birmingham 15. NORMAN L. CRABTREE.

REFERENCE

[1] Curtiss, E. S., *Lancet*, 1952, **1**, 989.

SIR,—The late Dr. E. S. Curtiss introduced the single-position method of anaesthetizing the nose in 1952. Reference to the anatomical diagram and radiograph in his article[1] will show that the volume of fluid recommended by Dr. R. I. Bodman and Mr. F. Boyes-Korkis (December 31, p. 1956) is unnecessarily large. Experience of Dr. Curtiss's method has shown that three minutes in the position described produces excellent anaesthesia and any blunt-ended angled needle will serve to introduce the 5 ml. of anaesthetic solution used.—I am, etc.,

The London Hospital, London E.1. G. P. FOX.

REFERENCE

[1] Curtiss, E. S., *Lancet*, 1952, **1**, 989.

Periodical Medical Examinations

SIR,—Dr. Michael H. K. Irwin (December 24, 1960, p. 1887) has placed high emphasis on the prophylactic value of periodical medical examinations. May I advertise their therapeutic benefit?

Very few of us, even the healthiest in mind and body, I submit, emerge from a searching medical examination without a feeling of elation at being informed that all our accessible organs are still intact and functioning normally; for we so frequently harbour a fear, born of some transient somatic dysfunction and varying in intensity from a stifled nagging doubt to a positive phobia, that all is not well. Fear is humanity's commonest disease. Isn't it fun being able to cure or alleviate it so simply?—I am, etc.,

Mundesley Hospital, Norfolk. GEORGE DAY.

Service Overseas

SIR,—The correspondence that has followed Dr. H. B. L. Russell's excellent letter (October 29, p. 1313) makes it clear that no prudent individual doctor can be advised to begin a career in medicine overseas. There are three main reasons: (*a*) the political risk, (*b*) difficulties in re-entry to medicine in Britain, and (*c*) the chance of having unacceptable colleagues of the kind described by Mr. V. B. Green-Armytage (November 12, p. 1449). All three reasons are valid, although (*b*) and (*c*) may be exaggerated.

The answer must surely lie in the export of medical teams rather than individual doctors. Units in this country could adopt units overseas and arrange to staff them under contract with the overseas government concerned. Individual members of the teams would come and go in rotation, but continuity of practice and clinical wisdom would be maintained. For example, Maternity Hospital X in England might arrange with the government of independent Arcadia to provide an obstetric team for 10 years to staff the lying-in ward of the new Blackville Hospital; the team would consist of an obstetrician, two registrars, and two midwives, whilst the local government would provide (for training) junior medical and nursing staff. The obstetrician-in-charge would either be a junior consultant, or the aspirant for the next vacancy, or even one of the more senior men public-spirited enough to set an example to others by doing a tour overseas. All these people would be part of the staff of the parent hospital and would return to their jobs there in due course. A similar arrangement could be made by laboratories, mental hospitals, surgical and medical units, public health departments, etc.

Something of this sort is already being done on a limited scale. Will some of your eminent correspondents set the ball rolling in their own hospitals and perhaps lead a team abroad themselves? The encouragement of government departments might help, but this is uncertain. Perhaps the B.M.A. would be a more suitable sponsor.—I am, etc.,

Brambridge, Hampshire. M. H. HUGHES.

Clinic Doctors

SIR,—It has been suggested in the correspondence on child psychiatry that part-time clinical assistants in child-guidance clinics might be paid for by the local education authorities (October 15, p. 1163). This would seem to be a quite unethical drain upon the all-too-small educational grants. We suggest that far more money could be spent upon staffing the child-guidance clinics at the expense of the infant-welfare clinics, where the presence of a doctor seems to be completely redundant and possibly harmful. Mothers of young children are actively encouraged to bring them to these clinics by the presence there of a doctor, by the provision of cheap milk, "marmite," "bemax," orange juice, and vitamins; and by the health visitor, whose definition of a really good mother is often the mother who "never misses the clinic." The children are weighed, their feeding problems discussed with the health visitor and other mothers, and it is, and should be, a pleasant social occasion.

If a child is well he does not need to see a doctor. If he is ill the clinic doctor is asked to see him. If at this interview there are any abnormal findings, the clinic doctor may not prescribe for or treat the child unless it happens to be one of his own N.H.S. patients (which is unusual, especially in urban areas). All he may do is write a letter, stating his findings, to the child's own doctor; then both child and mother must go through the whole procedure again with him. Moreover, the clinic doctor is well advised not to give any advice upon his findings, or upon behaviour problems, since if he does so the mother may become even more muddled by yet another and possibly different opinion, added to that of her friends, her mother-in-law, the district nurse, and her own doctor. Differences of opinion among doctors can hardly be wider than they are as regards infant feeding and child care. These differences, if expressed to the mother, may quite understandably result in lessening her confidence in doctors as advisers on child care as a whole.

The clinic doctors are well paid, and we cannot see that they are allowed to justify their existence at all. For surely the parents should be responsible for their own child in health, and their G.P. take on when the child is ill. For many a general practitioner, children and old people make up the bulk of his surgeries and visiting-lists. He surely would prefer to deal with them himself.—We are, etc.,

N. R. GARDEN.
B. K. ATTLEE.
ROSEMARY M. W. INCE.
Sutton Valence, Kent.

Control of Urinary Infections

SIR,—I am surprised that Mr. W. G. Q. Mills (December 24, p. 1884) has not yet heard of the eminently successful small-diameter polythene catheter invented by Mr. N. O. K. Gibbon, of the Liverpool Paraplegic Centre, Southport. I was one of the first patients on whom this catheter was used for prolonged bladder drainage in February, 1957, and can testify to its efficacy. I am a spinal paraplegic and required prolonged drainage at that time to clear up chronic infection. From the patient's point of view the catheter was eminently satisfactory.

May I refer Mr. Mills to an excellent article by Cosbie Ross, Gibbon, and Damanski,[1] of the Promenade Hospital, Southport, which was entitled "Recent Developments in the Treatment of the Paraplegic Bladder," and dealt very comprehensively with the subject? There seems no reason to suppose that the use of the polythene catheter described would be any different in the non-paraplegic bladder than it is in the automatic bladder of the paraplegic patient.—I am, etc.,

Headley Down, Hants. N. P. R. CLYDE.

REFERENCE

[1] Ross, J. Cosbie, Gibbon, N. O. K., and Damanski, M., *Lancet*, 1957, **2**, 520.

SIR,—Mr. W. G. Q. Mills (December 24, 1960, p. 1884) has rightly pointed out the need for a fine plastic catheter fitted with an inflatable balloon. This would be of great value in obese females and in males with scrotal swellings or obesity, in which cases external fixation of even a light plastic catheter[1] may prove difficult. Mr. Mills and others may be interested to know that Messrs. Wm. Warne and Co., Ltd., have supplied for trial a self-retaining plastic catheter (12 Charrière) with an inflatable rubber balloon which, though at an experimental stage, has given quite encouraging results. The drawbacks at present are that the cement joining the rubber to the plastic is somewhat unreliable, and that sterilization has to be carried out by ethylene oxide gas. I am hopeful that it will be only a matter of time before the technical difficulties are overcome.—I am, etc.,

Liverpool Regional Paraplegic Centre, Southport. NORMAN GIBBON.

REFERENCE

[1] Gibbon, N., *Brit. J. Urol.*, 1958, **30**, 1.

Radiological Hazards to Patients

SIR,—"Anonymous" (December 24, 1960, p. 1881) claims to identify an important radiological hazard—the radiologist. He wishes the Adrian Committee had taken steps to prevent general practitioners from referring their patients to radiologists "by-passing the out-patient department of the hospital and thus depriving the clinician [*sic*] of the chance of expressing his opinion." Clearly "Anonymous" does not consider either general practitioners or radiologists to be clinicians. This is false. Doctors in out-patient clinics, radiologists, and general practitioners are all clinicians. General practitioners could not practise modern medicine without direct access to ancillary aids. To deny them these is to waste their skill, to waste hospital beds, and to create a situation in which one group of doctors has a monopoly control over equipment. The examples quoted by "Anonymous" are no grounds in support of his argument. Hard cases make bad law.—I am, etc.,

The South-west London Mass *X*-ray Service, London S.W.6. F. A. NASH.

SIR,—I wish to protest against the remarks of your anonymous correspondent (December 24, 1960, p. 1881) concerning the use of *x*-ray facilities by general practitioners like myself. We are not mere clerks sign-posting every case that needs investigation to the nearest consultant.

I venture to suggest that general practitioners have enough clinical acumen to be able to determine which patients can be sent direct to the *x*-ray department, and furthermore can judge from the radiologist's report which patients can be dealt with by themselves and which require further investigation by a consultant. The example quoted by your correspondent appears to be an extreme case, and to suggest that general practitioners are adding to radiological hazards is in my opinion complete nonsense.—I am, etc.,

London E.3. BERNARD TAYLOR.

Electrocardiographs in General Practice

SIR,—We have carefully considered the letter of Dr. John W. Wigg (December 10, 1960, p. 1733) and would like to answer his several questions.

We have been using an electrocardiogram at the William Budd Health Centre since 1956 and find it very much worth while. It is a Philips Cardiolux model costing £296. With proper care in using it maintenance expenses can be reduced to a minimum. Only once in the four years has there been any need for a major overhaul, which was costly owing to the distance the representative had to travel. On other occasions the faults have been due to loose terminals which the sister can now adjust herself. All three nursing sisters at the centre very quickly learnt how to work the machine and can produce all the twelve leads required. It is small, compact, and portable, though its use is restricted to the centre as a matter of policy. It must be emphasized that the E.C.G. is limited in application as a diagnostic instrument and should be used only in association with clinical findings. It does not make a diagnosis by itself and, taken alone, a tracing can be very misleading. All the same we feel that it should be freely available to all G.P.s in common with other diagnostic procedures.

The most obvious saving is in the number of referrals to hospital out-patients; the E.C.G. is used two or three times a week (five firms, 12,000 patients at risk). On inquiry we find that this is comparable with hospital usage. We would hesitate to assess our competence to read the tracings, as we see relatively few, and for this reason we think it best to send all but the most obviously normal ones for consultant opinion. There is, however, no reason why any G.P. who wished to take the trouble should not become competent to read them himself. After all, we had to do this as students.

As to Dr. Wigg's first question whether we can use the E.C.G. with profit the answer is undoubtedly yes. We can deal now with most of our cardiac patients and maintain our clinical interest without having to refer them elsewhere. Out-patients profit because we save them a trip to hospital—a fair distance in our case. More important, we can get the result more quickly, and this is a great help in doubtful cases. There is also the psychological effect especially beneficial in "anxiety" cases. As for profit in its material sense, there is, of course, none. We do not charge for this service nor has it added a single patient to our lists. Its purchase for the individual practitioner is probably not justified, though a more widespread use would effect considerable

reduction in the price. It is certainly appreciated and used by all of us at this Health Centre.

We are informed that the manufacturers carry out a first-class maintenance service of two inspections annually for £10 10s.

—We are, etc.,

J. SLUGLETT. WILL SINTON.
H. I. HOWARD. D. H. FORSTER.
E. SAPHIER. K. M. HEWITT.
J. S. HUGHES GAMES. R. Y. CARTER.
E. J. LACE.

William Budd Health Centre, Bristol 4.

No Interview

SIR,—Like "Puzzled" (December 24, 1960, p. 1890), I am curious about the way in which London teaching hospitals select potential women medical students for interview. The particular case that interests me is that of a girl, also 18, with seven good "O" level passes (three over 80% marks), three "A" level passes, one at distinction level, one 74%, one 62%. She, too, was turned down by three London teaching hospitals without interview.

This experience, together with that of "Puzzled," is, of course, most reassuring. It is quite clear that the lady graduates of the older London teaching hospitals must be persons of Newtonian intelligence and of fantastically outstanding academic distinction, for not only have they been interviewed but even accepted after the interview.—I am, etc.,

Royal Infirmary, Manchester. D. LL. GRIFFITHS.

Oxford Medical School

SIR,—In his interesting Harveian Oration (December 24, 1960, p. 1821) Sir Francis Fraser states that after the establishment of clinical units in the London teaching hospitals, "there was little further development between the two world wars except for the appointment of a full-time professor of medicine at Bristol in 1935 and the establishment of the Postgraduate Medical School of London at Hammersmith." But what about Oxford? Two million pounds (and more) from Lord Nuffield, five clinical professorships with their departments, establishing a (mainly) postgraduate clinical school of some distinction. I am quite sure that Sir Francis's omission was due to a completely amiable slip of memory; but I hope future historians will not be misled. —I am, etc.,

Oxford. A. D. GARDNER.

POINTS FROM LETTERS

Radiological Hazards to Patients

Dr. JAMES F. BRAILSFORD (Birmingham 15) writes: I should like to give my full support to the letter signed "Anonymous" (December 24, p. 1881), which confirms the views expressed in an editorial in the *Journal of the International College of Surgeons* on "Roentgenograms: Their True Value to the Surgeon" (1960, **34**, 267). I should also like to comment on the letter by Dr. J. E. Parry (December 24, p. 1881). As a member of the Birmingham Medical School I would protest against his claim that they in Rhodesia "apparently give better service for minor injuries than you can get in Birmingham." I have no doubt that he and many others in Rhodesia endeavour to give patients the best treatment; but if he will consult the above-mentioned editorial he will see my reason for disagreeing with him.

Obituary

D. BAGSTER WILSON, O.B.E., M.D., M.R.C.P. D.T.M.&H.

Dr. D. Bagster Wilson, formerly director of the East African Institute of Malaria and Insect-borne Diseases, died suddenly at his home at Box, Wiltshire, on December 29, 1960, only a few months after he had retired from the East African Medical Service. He was 59 years of age.

Donald Bagster Wilson was born in 1901 and educated at Monkton Combe School, St. Catharine's College, Cambridge, and the Birmingham Medical School. Qualifying in 1926, he graduated B.Ch. at Cambridge in the following year and proceeded M.D. in 1935. Having taken the D.T.M.&H. in 1929, he joined the East African Medical Service in that year and was posted to Tanganyika. His first assignment was to make a short medical survey of the Africans of a coastal strip near Tanga. He was later appointed health officer to the Moshi–Arusha area of Tanganyika, and, in 1932, after a period of leave during which he married Dr. Margaret Elizabeth Lovett, a fellow student at Birmingham, he began what was to be his life work, the investigation of malaria, being given control of a newly constituted malaria unit at Tanga. The headquarters of this unit were later transferred to Old Moshi, and the survey work covered a wide area of the country until it was interrupted by the war.

Wilson joined the Army and was soon appointed to a malaria unit, attaining the rank of lieutenant-colonel and serving in Africa and Madagascar. After the war he continued his malaria work, and in 1949 he was appointed inter-territorial malariologist in charge of an East African malaria unit stationed at Amani, near Tanga; this unit was later expanded to become the East African Institute of Malaria and Insect-borne Diseases, and Wilson was its first director. The work involved research, teaching, and consultative work on malaria and other problems. After 10 years as director of this unit he retired in 1959, having been admitted M.R.C.P. in that year. He was appointed O.B.E. in 1953.

C. W. writes: Wilson's work, like his character, was consistent. He preferred to go deeply into a restricted field rather than to touch a wider field more superficially, and this characteristic—shared so completely by his wife, who was his close collaborator—was evident (as the writer remembers) from the first general survey near Tanga. There, and in his later malaria work, he examined relatively small numbers of people with great thoroughness, and later he and his wife, selecting the highly malarious village of Gombero as their observation area, month after month carried out the thousands of spleen and blood examinations, with tedious parasite counts, necessary to obtain a picture of the natural history of *Plasmodium falciparum* malaria at its highest intensity. The Wilsons had long been attracted to the epidemiological outlook of Christophers, James, Schüffner, and Swellengrebel, and appreciated and consistently emphasized the importance of acquired immunity in preserving the health of Africans in hyperendemic conditions, recognizing this not as a racial character (as had been supposed) but as a result of heavy and continuous infection. To disturb this immunity unduly, Wilson felt, might change the pattern to the detriment of the people, and he therefore advocated caution, giving minimum treatment so as to save life but to preserve immunity. He insisted that malaria in Africa is almost unique in its intensity, and that measures appropriate for India and elsewhere could not be assumed to be appropriate for Africa.

After the introduction of the residual insecticides Wilson organized widespread experiments—one very large one lasting several years in the Pare–Taveta area—which resulted in the finding that repeated spraying enormously reduced but did not eliminate infection. He remained reluctant to

base malaria work exclusively on chemicals, and continued to emphasize the human, nutritional, agricultural, and social factors which he regarded as essential to satisfactory progress.

Wilson did not avoid controversy. His intellect was tough and his attitude critical; he was not easily swayed, especially by fashion, but he earned the respect and admiration of the leaders of malariology throughout the world, and he had many friends, for he was amusing and hospitable, and liked company and good living. He had retired to his house in Wiltshire and was preparing to write a book on malaria, which would have been a masterpiece; he had much to say.

Dr. Margaret Wilson and his two daughters survive him.

W. E. M. WARDILL, M.B., B.S., F.R.C.S.

Mr. W. E. M. Wardill, who was professor of surgery at the Royal Medical College, Bagdad, from 1952 to 1958, and before that had been plastic surgeon to the Royal Victoria Infirmary and surgeon in charge of the department of prostatic surgery at the General Infirmary, Newcastle upon Tyne, died on December 24 at his home in Newcastle. He was 66 years of age.

William Edward Mandall Wardill came of north-country stock. Born at Gateshead, of which his father was a leading citizen, he was educated at the Newcastle Royal Grammar School and at Mill Hill School. After a short commercial interlude he became a medical student in Newcastle in 1913 and graduated M.B., B.S. in 1918. During the first world war he served as a surgeon-probationer in the R.N.V.R. and then, after graduation, as a temporary surgeon. Returning to Newcastle to complete his postgraduate education, he took the F.R.C.S. in 1920. He was fortunate in his early surgical training in that he had Rutherford Morison as a teacher, and later on was Grey Turner's house-surgeon. From the former no doubt he learned that didactic mode of instruction which was to make him such a successful teacher in his own right.

At the Royal Victoria Infirmary Wardill was appointed to the staff as assistant surgeon in 1929, having previously filled the post of surgical registrar there. In 1943 he became plastic surgeon at the R.V.I., and he held numerous other staff appointments at other neighbouring hospitals. At the medical school of the University of Durham he was assistant curator of the pathological museum and lecturer in surgical pathology from 1920 to 1946. Early in his career he undertook original work on cleft-palate surgery, and in many ways he considered his observations on wide pharynx in cases of cleft palate to be the most lasting of his contributions in this field. But his versatility as a surgeon was renowned, and whatever he did he did well.

For Wardill the approach to surgery was biological. Always an ardent field naturalist, he was intensely interested in form and function and their departures from the normal. He obtained a sound grounding in pathology as an assistant curator of the medical school museum at Newcastle, and, together with his colleague Dr. Whately Davidson, did a great deal to modernize and in fact renovate the collection. His first original work was carried out in association with Dr. James Whillis, the lecturer in anatomy, and from it grew Wardill's operation of pharyngoplasty. His pathological and surgical interests, however, were much wider than paediatric surgery or the congenital deformities. He was an accomplished general surgeon and made a number of forays into some of the more specialized fields, notably plastic surgery and the surgery of the prostate.

Nor were the excursions the casual interest of the dilettante. Wardill studied carefully whatever he took up, and even in these specialized branches he made noteworthy observations and contributions. He was one of the little group which James Spence gathered round himself to start the Babies Hospital in Newcastle. Most of Wardill's work in later years was done at the Newcastle General Hospital in the department of urological surgery, and at the plastic unit of the Shotley Bridge Emergency Hospital.

He emigrated to South Africa in 1948, but returned again to England two years later. Shortly after his return he accepted an invitation to fill the chair at the Royal Medical College in Bagdad, and there he spent six very happy and fruitful years. His great gifts as a teacher were given full scope, and he earned the devoted affection of his Iraqi students, who parted with him regretfully in the summer of 1958.

Apart from his distinction as a teacher and surgeon, Wardill was a man of wide interests in natural history, modern science, music, and even in archaeology. He was a fascinating talker, provocative, witty and imaginative, and always avid of new ideas, many of which came from his own active and lively mind. Whether his great gifts and talents were ever deployed to maximum advantage is a question which cannot now be answered. Two medical schools, one in northern England, the other in the Middle East, have reason to be grateful for his stimulating and formative influence upon many hundreds of students.

Mr. Wardill married Dr. Mary Russell Campbell, who died in 1942. In 1951 he married Mrs. Wilhelmina MacQueen, and she survives him, together with three sons and three daughters of his first marriage.

J. WHITBY, M.D., M.R.C.P., D.P.H., D.P.M.

With the death on December 13 of Dr. Joseph Whitby, general practice has lost a remarkable representative. He had practised in Willesden since 1928, and was 59 when he died. He was one of the outstanding bridge players of his day.

Joseph Whitby was born on December 22, 1900. He showed his outstanding quality from the start of his medical career, for he entered the Middlesex Hospital Medical School with an entrance scholarship and qualified M.R.C.S., L.R.C.P. in 1922 at the early age of 21. He graduated M.B., B.S. the following year, having obtained earlier distinction in organic chemistry. At this time he was awarded the Lyle gold medal and scholarship in surgery. He took the D.P.H. in 1924, the M.R.C.P. in 1926, and proceeded M.D. in 1927. By 1940, when he took the D.P.M., his interest in psychiatry had established itself.

After qualification he held various house appointments at Highwood Hospital, the King George V Sanatorium, Godalming, and the Victoria Park Hospital (now the London Chest Hospital), and then entered general practice in Willesden in 1928. Here he worked up to the outbreak of the second world war, when he served in the Emergency Medical Service as psychiatrist at Mill Hill Emergency Hospital and at the Maudsley Hospital. Returning to general practice after the war he became active in the Royal Society of Medicine as a prominent member of the Section of General Practice, and also in the College of General Practitioners, of which he was one of the founder members and chairman of the research group of the N.W. London Faculty. He contributed many papers to the medical journals and read papers at scientific meetings of the British Medical Association. He achieved well-merited prominence when in 1954 he was invited to serve on the Wolfenden Committee on Homosexuality and Prostitution. He was recently elected a member of the Middlesex local medical committee.

Joe Whitby's modest and self-effacing bearing concealed a truly extraordinary capacity, and the crowded and fruitful years of academic distinction by no means exhausted his intellectual energies, so that in another field, that of bridge, he acquired international fame, winning the Individual Masters' Championship in 1937 and the National Individual Championship after the war. He represented England in international competitions on many occasions. Characteristically, when he found bridge becoming an obsession to the detriment of his medicine, he abandoned it at the international level; and, equally characteristically, he was content to play in modest company for the fun of it.

With a self-disregard which was typical of this dedicated man, he continued to attend his wide and busy practice in the face of increasing exhaustion until a few weeks before his death, which came mercifully soon. He leaves a devoted wife and two sons, one of whom is in medical practice in Canada. To a host of patients, colleagues, and friends Joseph Whitby's premature death leaves a gap which will not easily be filled.—M. M.

H. L. PRIDHAM, M.R.C.S., L.R.C.P.

Dr. H. Llewellyn Pridham, who had to retire from practice in Weymouth many years ago because of ill-health, died suddenly at his home at Upwey on December 23. He was 67 years of age.

Hubert Llewellyn Pridham was born on September 10, 1893. His father, the late Dr. J. W. Pridham, practised at Broadwey, near Weymouth, from about 1860 until his death in 1899, and his elder brother, Dr. J. A. Pridham, still carries on the family practice. Llewellyn Pridham was educated at Weymouth College, St. Paul's School, London, and St. Bartholomew's Hospital, where he was a most popular student: many of his contemporaries will remember him as "Old Joe." Before qualifying in 1918 he had served in the R.N.V.R. as a surgeon-probationer in destroyers, and after qualifying he joined the Royal Navy as a surgeon lieutenant and went to the Far East. Resigning his commission in 1924, he held hospital residential appointments for a time and then contracted a mild attack of encephalitis lethargica which was not diagnosed at the time. Later in 1924 he entered general practice in Weymouth, but after three or four years signs of Parkinson's disease were becoming more apparent and he had to give up practice and retire to Upwey, where he lived until his sudden death from coronary thrombosis.

Before he became incapacitated his hobbies were fishing, shooting, sketching, and sailing. He was an enthusiastic member of the Weymouth Sailing Club, and the Llewellyn Pridham Cup is competed for annually. As the Parkinson syndrome developed he had to give up all these activities, and he began to write. *Chambers's Journal* published a series of 14 articles written by him, and he contributed to many other periodicals. His book, *The Dorset Coastline*, beautifully illustrated with photographs taken by Edwin Kestin, conveyed his deep feeling for his native county, and his excellent children's adventure story called *Purbeck Marble* was published as a book and broadcast as a play. Another play by him, *Trafalgar Days*, was also broadcast. After he had contributed to the *Lancet* series of articles written by patients he was interviewed by a Sunday newspaper, and as a consequence of this he was presented with an electric typewriter, which he found an enormous help, for loss of muscular power had made ordinary typing difficult. He was writing to the last: an article by him appears in the *Dorset Year Book*, just published, and his publisher had given him a hopeful report on his latest book.

Dr. Llewellyn Pridham married Kathleen (Kitty) Whiting in 1927, and she and their daughter Diana survive him.

D. R. S. writes: When I first met Dr. Llewellyn Pridham in 1946 he had already been unable to practise for 20 years, and yet I never thought of him as an invalid. Until the last he retained a lively interest in the outside world and was always ready for a game of chess, or to talk about anything but his health. It was a pleasure to visit him; as one of the very early members of the Weymouth Sailing Club he was always eager for news of the racing during the season.

He spent long hours a day working as a freelance journalist and author: as everyone knows, that leads to days of elation when one's work is accepted and weeks of frustration when publishers seem impossibly hard to please, but he always took the rough with the smooth, never boasting of the successes or complaining of the rejections.

Although he must have been infuriated by his increasing helplessness he never grumbled about it, and I shall always honour and remember him as one of the bravest men I have ever known. During the long years of decline he was cared for by his devoted wife, and it says much for them both that, in these difficult circumstances, their marriage was so completely happy. To her and to his only daughter may I express the sympathy of all the friends who share their loss.

J. S. FARNFIELD, M.R.C.S., L.R.C.P.

Dr. J. S. Farnfield, who practised in Hastings for 50 years, died in the Royal East Sussex Hospital on December 5, aged 83 years.

Born on September 12, 1877, John Stewart Farnfield was the son of Dr. W. E. Farnfield, of Brixton. Entering Guy's Hospital as a dental student in 1896, he qualified in dentistry two years later and obtained an appointment as dental officer to the Diamond Match Company in Liverpool in 1898. He held this appointment for four years, and during his tenure of it he was called to London to give expert evidence on "phossy jaw," an industrial hazard of the time. In 1902 he returned to Guy's to study medicine, qualifying M.R.C.S., L.R.C.P. in 1906. It had been his intention to take his Fellowship and practise surgery, but owing to ill-health he had to abandon this course, and instead joined his brother-in-law, Dr. Huckle, in partnership in Hastings, where he practised from the same house for fifty years. He had a special interest in the care of infants and children, and in 1917 became the first medical officer to the infant welfare centres which had been formed in Hastings by the Voluntary Service of Help for Motherhood and Infancy: in this capacity he gave devoted service for thirty years, ably assisted in this voluntary work by his wife, at the outset of her own long career of public service. In 1921 he pioneered the Halton antenatal clinic, the first to be opened in Hastings.

He was greatly loved by his patients, who relied upon him not only as a doctor but as an exceptional counsellor and friend. His free time was limited and occupied with the simple pleasures of gardening, bee-keeping, philately, and chess. His skill in diagnosis, above all in children, was based on the thoroughness of his examination of every case, and it might be said that he specialized in the closest observation and care of his patients—he was a true family doctor. Although during the last decade of his active work he limited his practice to the elderly, the passage of years did not diminish his inquiring interest in medical advances nor in the avidity of his medical reading up to the time of his last illness.

He is survived by his wife, who is an alderman of the borough of Hastings; his son, who is a solicitor; his step-son, who is a surgeon; and his niece, who for over 25 years was his dispenser and secretary.

ARTHUR CARR, M.R.C.S., L.R.C.P.

Dr. Arthur Carr, who practised in Stepney, died on December 2, aged 55.

Arthur Carr was born in London on February 14, 1905. From Davenant School he won an entrance scholarship to Guy's Hospital in 1922 and he qualified five years later. After some postgraduate experience he decided that general practice offered the most satisfying career in medicine, and he entered practice in Stepney in 1930.

H. E. O. writes: "The tragic death of Arthur Carr came as a great shock to his colleagues and innumerable friends. He was the embodiment of all that is finest in the general practitioner. An expert clinician and a painstaking one, he gave his whole time and experience to his large practice. He was a shining example of the family doctor, popular and beloved. His kind and understanding manner and his enormous sense of tolerance gained him the affection as well as the confidence of his patients. His kindness and his sense of humour were a tonic to all his friends.

He will be a great loss to Stepney, where his name was a household word and many will mourn his passing.

C. F. SHELTON, M.D., M.R.C.P., D.T.M.&H.

Dr. C. F. Shelton, who worked for many years as a medical specialist in Tanganyika before becoming deputy director of medical services in Uganda, died in hospital on December 9, aged 72.

Charles Frank Shelton (he changed his name from Schuler in 1920) was born on June 28, 1888. At St. Thomas's Hospital, where he qualified in 1910, he won the Treasurer's gold medal. After holding the post of house-surgeon at St. Thomas's he graduated M.B., B.S. in 1911 and then was senior obstetric house-physician at his teaching hospital and R.M.O. at the Samaritan Free Hospital. Thereafter he served as a civil surgeon in the Serbian Red Cross during the Balkan war and was awarded the order of St. Sava. Throughout the first world war he served as a temporary surgeon in the Royal Navy, being wounded at Gallipoli. He proceeded M.D. in 1916, took the D.T.M.&H. in 1924, and was admitted M.R.C.P. in 1930.

Shortly after demobilization he joined the Colonial Medical Service and was posted to the newly mandated Mesopotamia, transferring, in 1921, to Tanganyika, where he remained until 1939. During the greater part of his time in Tanganyika Shelton was in charge of the European Hospital at Dar-es-Salaam, first as medical officer and later as medical specialist, being the first in Tanganyika to hold the latter rank. He was president of the Tanganyika Branch of the B.M.A. from 1935 to 1937.

D. A.S. writes: All who were associated with East Africa between the two world wars will be grieved to learn of the death of Dr. Charles Shelton. As a medical practitioner he was exceptional. Primarily a physician, he had taken his M.D. in obstetrics and had acquired a great experience in that field. He was also an accomplished surgeon and for years in Dar-es-Salaam was obliged to undertake all the major surgery on European patients. There is no doubt that a man so versatile in his profession could have risen to the front rank in any branch of his choice had he adopted a less adventurous life and channelled his ability into a narrower field. In the event, he became the ideal general practitioner and as such was invaluable in a largely undeveloped country. To-day the young medical officer can look to specialist officers in almost every branch of medicine for help and guidance. Shelton could turn only to himself, with the rest turning to him.

In 1939 Shelton was transferred to Uganda as deputy director of medical services, and there was some speculation on whether a brilliant clinician would prove to be an equally good administrator. The views of members of the Uganda Medical Service who worked under Shelton at that time were unanimous. Under difficult war-time conditions Shelton became the model administrator. All problems were smoothed out quietly and efficiently, and it was said that the greater the flap the more calm he became; in all circumstances he remained completely unruffled. This was the most apparent feature of Shelton's character: it was unknown for him to show either excitement or temper, and this seemed to make him appear somewhat shy and reserved to those who had not the privilege of knowing him intimately.

To junior medical officers he was unfailingly kind and helpful and so became an almost legendary father-figure to whom all might turn in their difficulties and uncertainties. The term "father-figure" must be used with reserve, however, for Shelton was never patronizing. He treated all as his equals and was venerated accordingly. Outside his profession he had a great interest in history and had made a special study of the Napoleonic wars.

His professional career ended tragically. When preparing to return to Uganda from leave in England he suffered a double detachment of the retina, and, although he retained some degree of useful vision, he was obliged to retire from the service and spend the remainder of his life in retirement, though for a time he worked as assistant superintendent of the Zoological Gardens in Regent's Park.

The annals of the Colonial Medical Service are short, and perhaps the final chapter is drawing to its close, but in these annals the name of Charles Shelton has earned a sure and rightful pre-eminence. He will not be remembered for any special contribution to medical science but as the living exponent of the art and practice of medicine in its highest form. He would certainly qualify for the epitaph "Well done, thou good and faithful servant."

J. STEWART GOURLAY, M.B., Ch.B., D.O.M.S.

Dr. J. Stewart Gourlay's tragically sudden death on Christmas Day at the age of 52 has been a great shock to the district in which he practised. He was consultant ophthalmologist to the North Riding Infirmary, Middlesbrough.

John Stewart Gourlay was born on March 8, 1908, the son of Dr. J. Dickson Gourlay. He graduated M.B., Ch.B. at Leeds University in 1932, and after holding the post of house-surgeon at the Cheltenham Eye, Ear, Nose, and Throat Hospital he worked as clinical assistant at the Central London Ophthalmic Hospital and the Central London Ear, Nose, and Throat Hospital. He then joined his father in practice at Warrington, where he remained for some years. During the second world war he served in the R.A.F. with the rank of squadron leader. On his return to civilian life he decided to specialize in ophthalmology, and took the D.O.M.S. in 1949. He was appointed assistant ophthalmologist to the North Riding Infirmary soon afterwards, becoming full consultant there two years ago.

A. E. P. P. writes: Dr. J. Stewart Gourlay was a man of unusual charm and ability and worked in close association with me at the North Riding Infirmary, Middlesbrough, for ten years prior to my retirement in 1958, when he succeeded me as ophthalmic consultant. I greatly valued his help and judgment, and found his previous experience in general practice before specializing a great asset in his work as ophthalmologist, since it enabled him to handle his patients with uncommon understanding and consideration. He was a perfectionist in all he did, and brought an original and practical mind to bear upon his specialty. Only the best was ever good enough in his judgment, and to him the patient always came first. He was a man of varied interests, and to each of these he gave the same painstaking attention; as a sportsman, photographer, and gardener his achievements were always outstanding. His loss to ophthalmology in the north-east is very great, for he was taken at the very peak of his powers, and he will be sorely missed by his patients, colleagues, and friends, all of whom valued him as an ophthalmologist and equally as a man. Much sympathy will be felt for his widow and aged mother.

J. D. ROBERTSON, *M.C.*, M.B., Ch.B.

Dr. J. D. Robertson died suddenly on December 29 in a nursing-home in Swansea, where he was in practice until recently. He was 71 years of age.

James Dewar Robertson was born on April 7, 1889, the son of the Rev. Donald Robertson, of Glenlivet, Banffshire. Educated at the Grammar School and University of Aberdeen, he graduated M.B., Ch.B. in 1910. Thereafter he practised for a time in Ballindalloch, where he was also medical officer of health. During the first world war he served with distinction as medical officer with the 19th Battalion of the Machine Gun Corps and was awarded the Military Cross. He then joined Dr. Horatio Rawlings in Swansea and with his subsequent partners he developed one of the most flourishing practices in the area. During the severe air-raids which smote Swansea during 1941 and 1942 he was medical officer to the Sketty first-aid post, and his courage and resource will long be remembered.

A keen member of the B.M.A., he was also a Treasury medical officer and chairman of the Swansea National

Service Medical Board. Unsparingly he devoted his life to his patients, showing the skill, gentleness, and sympathy which made him such a beloved family practitioner. Worn-worn, he retired a year ago, but he remained cheerful and always ready to help the host of friends he had made in this area.

Dr. Robertson married Miss Katherine Balloan, who was his unfailing helpmate for so many years, and she survives him.—C. J. C.-J.

W. CORE, M.B., Ch.B.

Dr. William Core died at his home in Rotherham after a short illness. He was 83 years of age.

William Core was born on November 24, 1877, the son of the minister of Carrington, Midlothian. Educated at George Watson's College and Edinburgh University, he originally intended to follow his father into the ministry, and graduated M.A. in 1901. But, becoming attracted to medicine, he graduated M.B., Ch.B. in 1906 and practised for a time in his native land. Coming to England he was appointed house-surgeon at the Blackburn Infirmary.

In the first world war he served in the R.A.M.C. for four years, much of it throughout the Gallipoli campaign. On his return from war service he married Miss Margaret Farquhar, of Orkney, and settled in Rotherham, where he remained in practice till a short time before his last illness. Chairman of the Rotherham Division of the British Medical Association, he was a founder member and past-president of the Rotherham Scottish Association, being well known and highly esteemed in the local Scottish community. A man of striking simplicity and uprightness of character, he was tireless in his devotion to the large and busy practice in which he spent a long and honourable career. He will be long remembered and mourned by the many thousands of his patients, friends, and colleagues.

Dr. Core is survived by his wife and two daughters, one of whom, Dr. Jessica Core, is also a graduate of Edinburgh University and has ably assisted him in partnership for some years.—J. J. H.

FRANCES L. NICHOL, M.B., B.S.

Dr. Frances L. Nichol, for many years in general practice in Oxford, died on December 8 at the age of 61.

Frances Louisa Nichol was born in South Shields on December 12, 1898, the younger daughter of Lieutenant-Colonel W. D. Nichol, R.A. She spent most of her childhood in the North of England. She was educated at Bedford High School for Girls, and later became a medical student at the Royal Free Hospital in London, where she graduated M.B., B.S. in 1924. After serving in various hospital posts she worked for some time as an assistant to Dr. Tindall in Hurworth-on-Tees, where there are still some of her old patients who remember her with lively affection. In 1936 an assistantship in Oxford led to a partnership in which she remained until her death and in which she had built up a large and devoted practice. Obstetrics was perhaps her favourite work, and during the second world war she was in charge of a temporary maternity unit in Davenport House, Headington. Since that time she had also been one of the medical officers in the women's section of the venereal diseases clinic at the Radcliffe Infirmary.

Dr. Nichol's interests were not confined to medicine. She had green fingers in a garden and was a skilled embroideress. She was also a member of the parochial council of her church, St. Philip and St. James, and no account of her life would be complete without mention of her devotion in that sphere. In April, 1960, she was stricken with serious illness from which she never recovered but which she bore with extraordinarily calm courage. It must be a consolation to all her friends that she has been released from having further to endure.

With her death there has passed from the Oxford scene a general practitioner of whom it can truly be said that she was doctor and friend to all her many patients, whose affection and gratitude were shown endlessly during her last long illness.—I. L.

J. J. CREMIN, M.B., B.Ch., B.A.O.

Dr. J. J. Cremin, who died at Joyce Green Hospital, Dartford, at the age of 69, had practised in Crayford, Kent, for the past 20 years.

John Joseph Cremin was born on November 24, 1891, a native of Co. Limerick. He studied medicine at University College, Dublin, and graduated M.B., B.Ch., B.A.O., in 1915. After holding the post of senior house-surgeon at the Mater Misericordia Hospital, Dublin, he went into practice in Newcastle West, where he was medical officer to the County Home. After thirteen years there he came to England in 1929, and practised in Camberwell in South London. Later he practised in Crayford in partnership with his brother Maurice, who died two years ago.

W. P. J. P. writes: Dr. Joe Cremin will be remembered by his colleagues in Camberwell, where he practised for many years before leaving for Crayford in 1941. His rich Irish accent and heart of gold under a rugged exterior made him a striking figure at New Cross Society and B.M.A. Divisional meetings, in both of which he was an active member. His verbal encounters, in which Celtic sparks flew, with a Scottish member with an equally distinctive accent were most entertaining. A keen golfer, he was the first winner of the University College, Dublin, golf cup and a well-known member of the London Irish Medical Golfing Society. He was a sound general practitioner and a loyal colleague, and his passing will be deeply regretted.

He is survived by his wife, two sons, both of whom qualified at Guy's, and two daughters.

R. T. RAINE, *M.C.*, M.B., B.Ch.

Dr. R. T. Raine, who formerly practised in Stocksfield, Northumberland, died in hospital recently at the age of 70.

Reginald Thompson Raine was born on June 27, 1890. From the University of Cambridge he went on to St. Thomas's Hospital, where he qualified in 1915. After working as a casualty assistant at St. Thomas's he joined the R.A.M.C. and saw active service in the first world war, winning the M.C. and bar and being badly wounded in the leg. After the war he graduated M.B., B.Ch. at Cambridge, and then went into practice at Stocksfield-on-Tyne, where he remained for the rest of his life. He retired three years ago.

J. B. H. writes: In the death of Dr. Reginald T. Raine we have lost a great family doctor. I remember going to assist him for the first time during the second world war, when he had not had one half-day's break in a whole year in his large rural and suburban practice. Although overworked, he was always calm, methodical, and quite imperturbable. He had a deep sense of responsibility towards his patients and he believed being a doctor was a personal and continuous job.

He was a most competent general surgeon and was thus able to do a great deal for his patients. Many an acute abdomen he dealt with himself, and very well his patients did. His patients thought him to be inspired—and what contented patients they were.

Though suffering from a badly damaged knee, the result of a war wound, and giving a 24-hour service, I never knew him to have a tired mind, and he had the most delightful sense of humour. No matter how busy, he was always interested in the latest medical changes, and he was a keen attender at local medical meetings. His idea of a good holiday book was the latest edition of Samson Wright. His immense knowledge of practical medicine and his cultivated and intelligent mind made him a most inspiring teacher. I owe him a great deal.

Medico-Legal

COMMUNICATIONS BETWEEN DOCTORS

APPEAL TO HOUSE OF LORDS

[FROM OUR LEGAL CORRESPONDENT]

On December 21, 1960, the House of Lords delivered judgment on an appeal in an action brought against Dr. Jack Stephen Rix, general practitioner, of Mill House, Shenfield Common, Brentwood, Essex (*The Times*, December 22, 1960). The action was brought by the widow of a Mr. Chapman, a butcher who was accidentally wounded at work by a butcher's knife. At a cottage hospital Dr. Rix examined the wound to Mr. Chapman's abdomen. He concluded that, though the deep fascia had been cut, the wound had not penetrated the peritoneum. Dr. Rix sent Mr. Chapman home after the wound had been stitched and dressed. Dr. Rix told Mr. Chapman that he thought it was a surface wound, but he gave him an emphatic instruction to see his own doctor that evening and tell him what had been done. Mr. Chapman told his own doctor, Dr. Mohr, that he had been told at the hospital that the wound was "superficial," and Dr. Mohr diagnosed a digestive disorder. In fact, the wound had penetrated the small intestine, and Mr. Chapman died of acute peritonitis five days after the accident, after being admitted to hospital for an operation.

At first instance, Dr. Rix was found negligent on only one of the grounds charged against him—namely, that he had been negligent as a doctor in failing to communicate directly by telephone or letter with Mr. Chapman's own doctor after treating him. The Court of Appeal (one judge dissenting) allowed Dr. Rix's appeal against this finding.[1] The House of Lords, by a majority of three to two, dismissed Mrs. Chapman's appeal and upheld the Court of Appeal's finding in favo. " of Dr. Rix.

Nature of Message

The majority of the House of Lords took the view that, although the patient would be expected to pass on the reassuring part of Dr. Rix's message, that did not cancel out the main part of the message, which was an emphatic warning that the patient's own doctor should be called in. If Dr. Rix had communicated with Dr. Mohr directly, he might have said that Mr. Chapman needed watching, but Dr. Mohr could be expected to understand that without being told.

Of the minority of the House of Lords, Lord Keith took the view that Dr. Mohr should have been put in possession of information on what had been observed and done by Dr. Rix; and Lord Denning is reported by *The Times* as saying:

> A medical man might sometimes feel justified in giving misleading information to a patient so as not to worry him. But if he did so, he must be very careful to give the true information to his relatives and to those about him, and, most important of all, to the patient's own doctor who had to treat him.

No Precedent

The judges in this case were sharply divided, not so much on questions of law as on the application of the law to the facts of the case. The doctrine of precedent applies only to statements of law. The decision in this case is not authority for the proposition that a doctor (whether a general practitioner or casualty officer) who treats a patient in an emergency is never under a duty to write to the patient's own doctor if he thinks observation is advisable. There are patients so lacking in intelligence that any message given to them orally could not be expected to be delivered accurately. There are other patients who can be expected to deliver a message accurately but whom it is necessary to reassure, with the result that an oral message may be over-optimistic at first sight: the greater the degree of reassurance, the less urgent is the message. There are so many gradations of facts that the question whether to write is a most difficult one; but the only safe policy to adopt is always to communicate directly with the patient's own doctor in all cases where further observation is advisable.

The decision contains a warning for general practitioners that, when a patient comes to them on the instructions of another doctor after treatment for an emergency, any reported reassurances should be treated with reserve.

[1] *Brit. med. J.*, 1959, **2**, 1190.

Universities and Colleges

UNIVERSITY OF CAMBRIDGE

Dr. I. M. Glynn has been reappointed a University Demonstrator in the Department of Physiology with tenure from April 1, 1961, for two years, and Dr. L. H. H. May has been reappointed a Health Service Officer with tenure from May 1, 1961, for five years.

In Congregation on December 13, 1960, the degrees of M.B., B.Chir. were conferred on H. M. James (by proxy) and J. A. Dyde (in person).

The following candidates have been approved at the examinations indicated:

FINAL M.B.—*Part II*: [1 2]T. C. M. Andrews, [1]D. R. Bainbridge, [1 2]J. K. Bamford, [2]M. H. Bartlett, [1]P. F. Bates, [2]B. Blackwell, [2]R. W. Blamey, [2]W. K. Blenkinsopp, [2]W. J. Boerema, [2 3]P. N. Booth, [1]I. F. Brockington, [2]N. M. S. Brown, [2 3]M. T. T. Bryant, [2 3]C. C. Chan, [1 2 3]J. M. Charlton, [1]H. Cheng, [1]M J. Dennam, [1 2 3]T. F. C. Dibble, [1 2 3]M. C. Doddridge, [1]P. A. Draper, [1 2 3]J. H. J. Durston, [1]J. R. Eames, [3]R. H. Eleady-Cole, [3]J. R. H. Fisher, [2]A. E. Forbes, [2 3]A. E. Gent, [2]S. L. Geoghegan, [1 2]D. F. Gibson, [2]A. J. Gordon, [2]W. D. Graham-Brown, [1 2 3]E. J. W. Gumpert, [1 2]G. Hamber, [1]J. W. Hamilton, [2 3]P. S. E. G. Harland, [2 3]W. D. Harper, [1]P. W. Harvey, [2]A. R. H. Hastie, [1]L. J. H. E. Hayek, [1 2 3]M. Hayward, [1]L. D. Heap, [2]G. D. Ingram. [2 3]A. J. Johnston, [1 2]R. A. Knight, [1 3]M. J. Leverton, [1]R. K. Mackenzie Ross, [1]I. C. McLellan, [2]C. N. Mallinson, [1]B. R. Middleton, [2]R. S. Moore, [1 2]D. Pye, [1 2 3]J. P. Recordon, [2]M. H. C. Rice, [2]Mrs. J. M. Robson. [1 2]Mrs. W. D. Savage, [1 2]R. B. Sellwood, [2]T. H. Spreadbury, [1 2 3]J. D. Swales, [2]F. J. B. Taylor, [2]J. H. Thornley, [2]P. E. Walker, [2]F. W. Webb, [2 3]R. C. Westbury, [2]A. J. Whitworth, [2]E. D. G. Williams, [2 3]J. D. S. Wilson, [2]G. H. E. Woodbine, [2 3]L. I. Zander. *Part I (Pathology and Pharmacology)*: P. W. Adams, E. J. Anderson, D. R. Aubrey, P. R. H. Barbor, R. S. Bartholomew, N. M. Bassett, J. S. M. Beales, P. G. Beauchamp, C. C. Black, R. D. Blackledge, D. I. Bowen, J. E. Bowen, J. B. Brown, G. T. Bungay, J. K. Butler, D. W. Cairns, C. H. Cameron, S. Channell, R. H. G. Charles, J. R. Chesterton, J. B. Cocking, N. K. Coni, C. K. Connolly, D. Cook, F. B. Cookson, P. E. Copus, A. G. L. Corkill, A. V. Cowan, R. J. Cryer, J. S. Cunningham, C. Dare, R. S. Dean, F. T. de Dombal, R. S. Deraniyagala, J. W. D. Drake-Lee, R. A. Durance, N. A. Dyer, G. M. Eames, A. M. Edwards, R. H. Eleady-Cole, D. E. Elgar, D. J. Evans, J. G. Evans, A. N. Fawcett, W. R. F. Ferguson, E. S. Field, H. L. Firth, H. M. Fischer-Webb, J. A. Fixsen, O. J. Follows, G. J. J. Fuzzey, J. R. C. Gardham, D. Gardner-Medwin, D. W. Gau, A. E. Gent, D. G. Gibson, T. A. Glanville, C. M. T. Gleave, K. E. Gray, F. R. Greenlees, C. J. Griffiths, E. J. W. Gumpert, J. W. Hamilton, C. P. Heanley, R. L. Himsworth, N. E. H. Holmes, E. M. Holt, J. B. Houghton, W. N. Hutton, D. M. Hynes, N. Jankey, A. E. Jephcott, G. J. Johnson, E. W. L. Jones, T. G. Jones, J. E. A. Knowles, H. H. M. Knox-Macaulay, R. C. Lallemand, S. Y. Lee, J. Lendrum, G. D. Loft, I. L. Mackenzie, R. K. Mackenzie Ross, N. C. Macmillan, J. R. Maltby, A. P. Manasse, R. W. Marcuson, J. R. Marlar, J. J. Meanley, A. J. B. Missen, M. C. W. Morgan, J. O. Morgan-Hughes, M. T. Morrell, P. H. W. Mylechreest, J. B. Newth, P. J. Noble, W. J. Norman, S. Nundy, D. H. Orrell, J. P. A. Page, J. W. Partridge, W. M. P. Patterson, H. J. Pendleton, I. Phillips, G. Pincherle, D. M. Potts, T. D. Preston, R. D. Pyrah, P. H. Rees, A. B. Richards, M. T. S. Roberts. A. P. Rubin, J. E. L. Sales, M. N. Sampson, J. H. Sandford-Smith, K. B. Saunders, G. L. Scott, P. V. Scott, S. L. Sellars, E. H. Shaw, J. J. Shenkman, M. A. Shirley, I. S. Smith, M. C. Storey, J. E. O. Sunkwa-Mills, M. Tarrant, A. B. W. Thomas, G. E. R. Vaughan, E. R. Verrier-Jones, P. R. J. Vickers, C. D. Walker, P. J. Watkins, R. H. Weeks, R. C. Westbury, J. A. B. Weston, O. C. Wetherell, D. G. Wilkins, H. T. Williams, E. B. Wilson, A. D. Wright, I. Ziment.

[1]Passed in principles and practice of physic. [2]Passed in principles and practice of surgery. [3]Passed in midwifery and gynaecology.

UNIVERSITY OF ABERDEEN

The following resignations are announced: Mr. Ian MacGillivray (Senior Lecturer in Midwifery), as from May 31, 1961, on being appointed to the Chair of Obstetrics and Gynaecology at St. Mary's Hospital Medical School, University of London; Dr. Kenneth B. Fraser (Senior Lecturer in Bacteriology), as from March 31, 1961, on being appointed to a lectureship in the new Department of Virology in the University of Glasgow; and Dr. Mark S. Fraser (Lecturer in Child Health), as from January 15, 1961, on being appointed Consultant in Medical Paediatrics in East Fife, under the South-eastern Regional Hospital Board.

UNIVERSITY OF DURHAM

At a Congregation held on December 17, 1960, the following degrees and diplomas were conferred:

M.B., B.S.—P. C. Ahluwalia, R. H. Appleby, G. H. Cowling, D. D. Imrie, J. N. Mitchell, E. W. Nave, P. T. F. Newman, E. E. O. H. Okeke, *A. Potter, *G. E. Rich, H. M. Sanderson, Elizabeth B. Taylor, B. Thalayasingam, P. T. Vale, A. C. Watt.

DIPLOMA IN PSYCHOLOGICAL MEDICINE.—Eileen Atkinson, B. Cornes, K. Davison, Agnes W. Justice, H. Neubauer, Joan M. Ridley, F. J. Roberts, C. K. Sutcliffe.

*In absentia.

Vital Statistics

Influenza

Compared with a year ago, deaths from pneumonia and bronchitis in England and Wales began to show a moderate rise from the week ended December 17, 1960. Deaths attributed to influenza showed a rise of from 23 in the week ended December 24 to 45 in the week ended December 31. In the last week of 1959 there were 24 deaths from influenza. The Ministry of Health has received reports from several districts in the Midland region of local outbreaks of influenza-like illness which began in the week ended December 24.

We are indebted to Dr. C. W. GORDON, S.A.M.O., Birmingham Regional Hospital Board, for the following report: Evidence of bronchiolitis in children resident in the City of Birmingham admitted to hospital was followed immediately before Christmas by a sharp rise in the number of cases of respiratory-tract infection in the adult population admitted to hospital. Within a week there were indications from hospital admissions that this infection was present in the Black Country and Wolverhampton conurbation and Coventry and Nuneaton, and within a further week that it had occurred in the periphery of the hospital region, including Stoke and Stafford in the north and Worcester and Hereford in the south. Hospitals have been under very heavy pressure from admissions of such cases with chest complications, including bronchopneumonia, a few cases of haemorrhagic pneumonia, and cardiac disease. The elderly and those with chronic bronchitis have also figured in hospital admissions. As a measure of admissions in the City of Birmingham, the Birmingham Bed Bureau's daily case load has been double that of the corresponding period 12 months ago. Nursing staff of hospitals have been affected with respiratory-tract infection necessitating off-duty for up to 4–5 days. Clear definition of infection has been complicated by the number of cases of respiratory disease expected in a community at this season of the year. Nevertheless, many patients at hospital presented signs and symptoms of clinical influenza.

The Regional Virus Laboratory, Little Bromwich General Hospital, Birmingham, reports 10 isolations from hospital patients and nurses, resident in the City of Birmingham, of a virus closely similar to or identical with the Asian influenza virus. The laboratory has also found serological evidence of influenza A infection in 19 hospital patients resident in the City of Birmingham.

Diphtheria in Camberwell

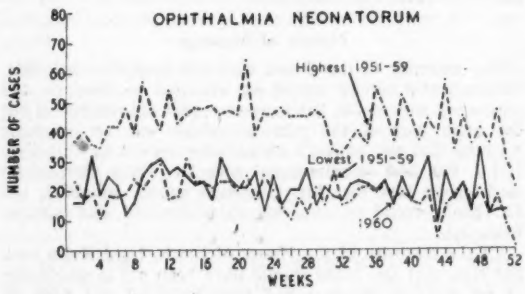
We are indebted to Dr. H. D. CHALKE, Medical Officer of Health, Camberwell, for the following report: On December 19, 1960, a Camberwell child, a patient at a London children's hospital, was notified as suffering from faucial diphtheria. The child, aged 7 years, became ill on December 15 but was at school on December 16. The school closed for the Christmas holidays on December 21. Since then 11 cases of clinical diphtheria and 19 children found to be harbouring the organism (*C. diphtheriae mitis*) have been admitted to hospital. In January, 1960, 76 cases and carriers were discovered in another part of the borough, but there is little evidence of a connexion between the two outbreaks. The present cases have tended to be less mild in character, and some of the children have had severe attacks of the classical type. There has been one death.

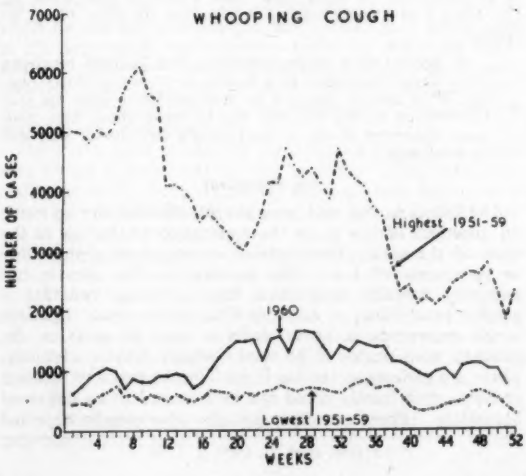
The outbreak is linked with a primary school, and nearly all those affected are pupils there; the others attend an adjoining junior mixed school or are family contacts. Most of the children are aged 6 years. Cases are so far limited to an area of about ¼-mile radius round the school. In only one of the patients is there a record of immunization, but there had been no reinforcing injection.

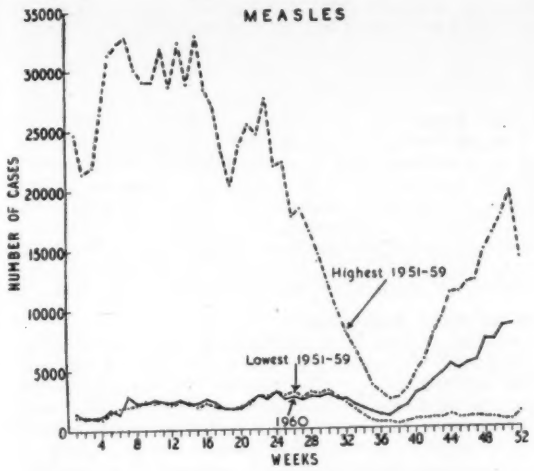
Most of the subsequent cases and carriers were brought to light as a result of swabbing and surveillance of class and home contacts, which, though complicated by the school holiday, was begun immediately. General practitioners, who were alerted at once, were also given suggestions on immunization procedures. They gave the fullest co-operation. As a result of home visiting, and the publicity in the press and the broadcasting services, there has been a welcome increase in the numbers immunized. Apart from the active or passive immunization given to the contacts of the first cases, large numbers of children have been brought to the special clinics established at the school, as well as to the regular sessions in other parts of the borough. It is too early to say whether these energetic measures have been successful in quenching the outbreak, but it seems that more cases may be expected.

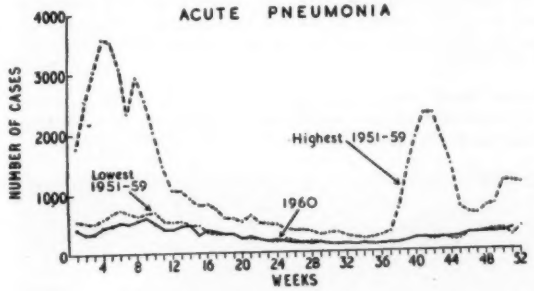
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the years 1951–9 are shown thus ------, the figures for 1960 thus ———. Except for the curves showing notifications in 1960, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

Areas where numbers of notifications were high in the latest two weeks for which figures are available.

	Week Ending Dec. 24	Week Ending Dec. 31
Measles		
Durham	368	**419**
South Shields C.B.	63	**105**
Lancashire	1,801	**2,147**
Blackburn C.B.	100	**122**
Bolton C.B.	151	**230**
Liverpool C.B.	249	**219**
Manchester C.B.	126	**244**
London	726	**910**
Islington	97	**118**
Nottinghamshire	562	**621**
Nottingham C.B.	113	**217**
Oxfordshire	115	**200**
Oxford C.B.	112	**175**
Suffolk	203	**211**
Ipswich C.B.	135	**131**
Warwickshire	275	**430**
Birmingham C.B.	170	**254**
Coventry C.B.	67	**121**
Yorkshire West Riding	714	**1,026**
Bradford C.B.	129	**190**
Leeds C.B.	149	**166**
Rawmarsh U.D.	43	**113**
Glamorganshire	346	**464**
Swansea C.B.	230	**250**
Diphtheria		
London	1	**17**
Camberwell	1	**17**

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **December 24** (No. 51) and corresponding week 1959.

Figures of *cases* are for the countries shown and London administrative county. Figures of *deaths* and *births* are for the whole of England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria	2	1	0		1	2	0	2	0	2
Dysentery	544	42	81	15	4	683	110	122	5	3
Encephalitis, acute	1	0		1		5	0		0	
Enteric fever:										
Typhoid	1	0	0	0		1	0	0	1	
Paratyphoid	1	0	1(B)	0		4	0	0	0	4(B)
Food-poisoning	89	15	12	2		164	10	6	0	
Infective enteritis or diarrhoea under 2 years				15	17				4	18
Measles*	8,601	726	51	97	115	948	18	21	3	17
Meningococcal infection	19	0	0	0	2	14	2	7	1	
Ophthalmia neonatorum	13	3	1	0		8	1	3	0	
Pneumonia†	356	28	222	2	3	233	19	200	2	
Poliomyelitis, acute:										
Paralytic	4	1	1	0	2	1	0	0	0	1
Non-paralytic	1	1	0	0		1	1	0		
Puerperal fever§	121	24	9	0		125	13	4	0	1
Scarlet fever	441	27	49	19	16	1,001	47	91	9	23
Tuberculosis:										
Respiratory	314	53	49	12		262	38	45	5	
Non-respiratory	42	6	14	2		31	2	8	3	
Whooping-cough	731	40	102	3	25	371	42	93	3	24

DEATHS	1960 Eng. & Wales	1960 Lond.	1960 Scot.	1960 N. Ire.	1960 Eire	1959 Eng. & Wales	1959 Lond.	1959 Scot.	1959 N. Ire.	1959 Eire
Diphtheria	0	0	0	0		0	0	0	0	
Dysentery	0	0		0		0	0		0	
Encephalitis, acute		1					0			
Enteric fever	0	0	0	0		0	0	0	0	
Infective enteritis or diarrhoea under 2 years	10	0	1	0		13	0	0	0	
Influenza	23	0	0	1		17	0	0	0	
Measles		0	0	0			0	0	0	
Meningococcal infection		1	0				0	1		
Pneumonia	792	56	17	33		480	42	27	9	
Poliomyelitis, acute	1	0		0		2	0		0	
Scarlet fever		0	0	0			0	0	0	
Tuberculosis:										
Respiratory	79	4	8	0		63	4	6	1	
Non-respiratory		0	0	0			1	0	1	
Whooping-cough	0	0	0	0		1	1	2	0	
Deaths 0–1 year	397	42	35	6		270	33	30	4	
Deaths (excluding stillbirths)	13,285	1003	686	213		8,967	652	607	123	
LIVE BIRTHS	13,078	1097	942	239		8,409	775	705	164	
STILLBIRTHS	302	22	25			189	14	20		

* Measles not notifiable in Scotland, whence returns are approximate.
† Include primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Medical News

World Medical Periodicals

The third edition of *World Medical Periodicals* (published by the World Medical Association) is now being prepared in the editorial office of the *British Medical Journal*. A circular letter has been sent to the editors of the periodicals listed in the second edition (published in 1957), but particulars of some 1,300 periodicals have not yet been returned. Editors who have not received the circular letter or who have not yet replied to it are asked to send a specimen issue of their periodical by airmail to Mr. C. H. A. FLEURENT, L.-ès-L., *World Medical Periodicals*, c/o *British Medical Journal*, B.M.A. House, Tavistock Square, London W.C.1, England, and paste on the cover a typewritten slip giving (1) the address of the publisher if different from that of the editorial office, (2) the language(s) of the original articles (not of the summaries), and (3) the number of parts published each year (12=a monthly journal; x=an irregular publication).

Nuffield Travelling Fellowships for G.P.s

Nuffield Travelling Fellowships have been awarded to Dr. M. B. LENNARD (Bristol) to visit Canada and the U.S.A. to study social and environmental factors in both undergraduate and postgraduate training in medicine; Dr. R. A. B. RORIE (Dundee) to visit Canada and the U.S.A. to study general practice, with special reference to the incidence and treatment of the psychoneurotic and early psychiatric case, for comparison with incidence and treatment under the National Health Service; Dr. P. A. T. WOOD (Ipswich) to visit the U.S.A. to study techniques and treatment of the respiratory viruses in general practice; and Dr. J. C. YEATMAN (South Australia) to spend six months visiting medical centres in Canada, the U.S.A., and Great Britain during 1961.

Tring Isolation Hospital

The auction of Tring Isolation Hospital is to take place in the near future, though the date and the place of the auction have not yet been fixed. The hospital was given to the town by the Rothschild family at the beginning of the century and was taken over by the Ministry of Health in 1948. The building has not been used as a hospital under the National Health Service, as it was considered unsuitable for the purpose, and it has now been offered back to the council by the Ministry at a price of £5,000. The council has refused the offer, contending that the building should be returned to the town on the terms and in the condition in which it was taken.

"Health at Work"

More than 300 million working days are lost each year in Great Britain because of sickness or injury, says the foreword to *Health at Work*, a Ministry of Labour publication on industrial health schemes. It describes 14 examples of such industrial schemes operating in different types of factory in various parts of the country. Fear about costs is suggested as being the biggest single factor in preventing the more rapid spread of industrial medical services, and detailed figures are therefore given of the cost of each of the schemes. Of the 14 described, seven cost £2 or less per head a year, five between £2 and £3, and two over £3. The booklet, though not on sale, is being distributed to factories, and inquiries are being dealt with by the Chief Inspector of Factories, Ministry of Labour, St. James's Square, London S.W.1.

Slough Industrial Health Service

In 1959 to 1960 the Slough Industrial Health Service increased its membership to 205 firms with 19,700 employees. From a population at risk of 19,700 there were 2,399 eye incidents due to occupational causes, representing a loss of over 3,000 man hours for this single preventable condition. An approach was made during the year to a London teaching hospital and medical school to see if the school would be interested in providing accommodation for an independent industrial hygiene unit. Preliminary discussions are now in hand. (*Thirteenth Annual Report*, 1959–60.)

Scientific Film

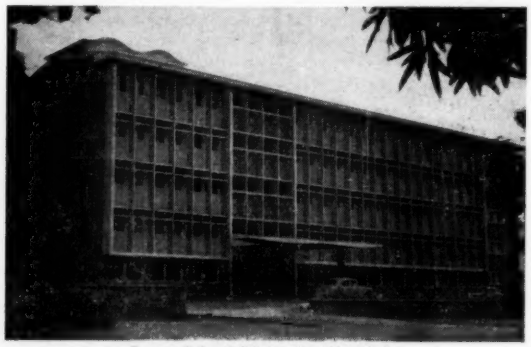
The Department of Scientific and Industrial Research has set up a working party to consider national needs in the field of scientific film. It is especially interested in the aspects of film as a research tool and in communicating research results. The working party includes Mr. C. ENGEL (Medical Illustration Department, Guy's Hospital), Professor G. E. H. FOXON (Guy's Hospital), and Professor C. H. WADDINGTON (Institute of Animal Genetics, Edinburgh).

"Filled Milk" Regulations

Regulations controlling the labelling and advertising of "filled milk" (skimmed milk with added non-milk fat) will come into operation on September 19. Certain descriptions must be used on labels and in advertising, and some products must be labelled with a declaration about feeding them to babies. Labels which carry a claim in relation to coronary disease must bear also a statement about the kind and amount of fat used. The provisions about baby feeding and coronary disease have been recommended or endorsed by the Committee on Medical and Nutritional Aspects of Food Policy.

Lagos Island Maternity Hospital

A new maternity hospital, costing £500,000, has recently been opened in Lagos. The hospital has 227 beds and 192 cots,



Lagos Island Maternity Hospital.

and is staffed by 15 doctors and 330 members of the nursing staff, including pupil midwives. The average duration of stay in the hospital is four or five days. (Photograph by courtesy of the Medical Superintendent, Dr. J. A. Sodipo.)

"Hospital Abstracts"

The Ministry of Health is publishing *Hospital Abstracts*, a new monthly survey of world literature relating to hospital matters and based on the Ministry's library. The publication will be linked with an abstracting service. (H.M.S.O., single issue: 5s.; annual subscription, including postage: 64s.)

Eli Lilly Medical Research Fellowship (South Africa)

Applications are invited from medical practitioners registered in South Africa for the 1961 award of this Fellowship. The Fellowship is for medical research and is not intended for postgraduate clinical study. Its net value is $300 a month for 12 months, plus return travelling expenses to the point of study in the United States of America. Details can be obtained from Dr. H. A. SHAPIRO, P.O. Box 1010, Johannesburg, South Africa. The closing date for applications is May 1.

Royal Society of Medicine's Anaesthetics Prize

The Section of Anaesthetics of the Royal Society of Medicine is offering a prize of £30 for the best paper on a

subject of the author's choice but connected with anaesthesia, written by a medical practitioner of senior registrar or registrar status in the National Health Service holding a clinical appointment in anaesthesia. He need not be a Fellow of the R.S.M. Further details can be obtained from the Honorary Secretary, Section of Anaesthetics, Royal Society of Medicine, 1 Wimpole Street, London W.1. The closing date for the 1962 award is January 1, 1962.

Treacher Collins Essay Prize

The Ophthalmological Society of the United Kingdom has instituted a Treacher Collins Prize Essay of £100 to be awarded triennially to a qualified medical practitioner of any nationality for the best essay submitted in English upon a subject chosen by the Society's Council. The subject for the next award is "Demyelination and the Eye," and essays should be submitted by December 31, 1962, to the Honorary Secretary, Ophthalmological Society of the United Kingdom, 47 Lincoln's Inn Fields, London W.C.2, from whom details may be obtained.

Perse School, Cambridge

Medically qualified Old Perseans, who, now that the Perse School has moved to new premises, would like to contribute to honouring the founder, Dr. Stephen Perse (1548–1615), a Cambridge physician, are asked to send their contributions to Dr. J. A. FRAIS, 16 Carr Lane, Shipley, Yorkshire.

Grants, Gifts, and Bequests

A trust fund of about £30,000 is to be administered by the Edinburgh University Court for research into the causes and treatment of malignant disease, and, in particular, for the provision of fellowships or travelling scholarships for this purpose. The fund has been made available by the Cancer Control Organization for Edinburgh and South-East Scotland, and is to be named the J. J. M. Shaw Cancer Research Fund in memory of the organization's first chairman.

The Medical Research Council has made a grant of £37,484 to Edinburgh University for the development of a programme of research on the experimental and clinical problem of transplantation under the direction of Professor M. F. A. WOODRUFF in the department of surgical science.

Director-General, Army Medical Services

Major-General H. E. KNOTT will succeed Lieutenant-General Sir ALEXANDER DRUMMOND as Director-General, Army Medical Services in April (*corrected announcement*).

People in the News

Surgeon Captain P. DE B. TURTLE, R.N.R., has been appointed honorary surgeon to the Queen in succession to Surgeon Captain J. A. SHEPHERD, R.N.R.

Major-General A. MENECES, late R.A.M.C., has been appointed honorary physician to the Queen in succession to Major-General W. D. HUGHES, retired.

Sir CECIL WAKELEY has resigned the presidency of the Lord's Day Observance Society, a post he has held for 14 years. (*The Times*, January 5.)

Brigadier (temporary Major-General) W. A. ROBINSON, late R.A.M.C., has been appointed honorary surgeon to the Queen in succession to Brigadier J. E. SNOW, retired.

Sir STEWART DUKE-ELDER, F.R.S., has been appointed Bailiff Grand Cross of the Order of the Hospital of St. John of Jerusalem.

COMING EVENTS

Oxford Graduates Medical Club.—Winter dinner, January 20, Royal College of Physicians, Pall Mall, London S.W.1. Chairman: Dr. L. N. JACKSON. Applications to Miss JOSEPHINE BARNES, 7 Wimpole Street, London W.1, by January 16.

British Association of Allergists.—Annual general meeting, including symposium on "Farmer's Lung," January 28, 11 a.m., Royal Society of Medicine, 1 Wimpole Street, London.

Royal Medico-Psychological Association: Maudsley Bequest.—Two-day lecture course, February 13 and 14, Royal Society of Medicine, 1 Wimpole Street, London W.1. Details from, and applications for tickets to, Secretary, R.M.P.A., 11 Chandos Street, Cavendish Square, London W.1.

Central Council for Health Education.—Annual seminar for medical officers, "Mass Media and the Medical Officer of Health," including symposium on "Television," February 21–24. Applications to Medical Director, C.C.H.E., Tavistock House, Tavistock Square, London W.C.1.

Royal College of Obstetricians and Gynaecologists.—Symposium, "Recognition and Treatment of Foetal Abnormality," March 24, at the College, Sussex Place, Regent's Park, London N.W.1.

Association of Surgeons of Great Britain and Ireland.—Annual meeting, Bristol, April 6–8. Discussions will include "Organ Transplantation" and "Trauma." Details from Honorary Secretary, at 47 Lincoln's Inn Fields, London W.C.2.

Medical and Scientific Section, British Diabetic Association.—Spring meeting, April 7, 8, University College Hospital, London W.C.1. Members and others wishing to present papers should write to the Secretary of the Section, British Diabetic Association, 152 Harley Street, London W.1.

7th Symposium, European Association against Poliomyelitis.—Oxford, September 17–20. Applications to attend to Dr. P. RECHT, Secrétaire Général, 56 Rue Charles Legrelle, Bruxelles 4, Belgium. Those wishing to read papers should communicate with the Secretary, United Kingdom Committee for Poliomyelitis, Royal College of Physicians, Pall Mall East, London S.W.1, by March 1.

NEW ISSUES OF SPECIALIST JOURNALS

The journals listed below are obtainable from the Publishing Manager, B.M.A. House, Tavistock Square, London W.C.1.

THORAX

Pulmonary Embolism. P. R. Allison, M. S. Dunnill, and R. Marshall.
Brain Damage in Children after Deep Hypothermia for Open-heart Surgery. Viking Olov Björk and Gösta Hultquist.
Blood Coagulation Problems in Open-heart Surgery. P. Fantl and H. A. Ward.
A Technique for Transeptal Left Heart Catheterization via the Right External Jugular Vein. S. Bevegård, E. Carlens, B. Jonsson, and I. Karlöf.
Blood and Electrolyte Balance in the Post-operative Cardiac Patient. M. V. Braimbridge.
Excision of Saccular Aneurysm of the Thoracic Aorta: A Report of Five Cases. B. J. Bickford and J. S. Glennie.
Arrhythmias Following Cardiac Surgery. R. W. Emanuel.
Pulmonary Infarction in Disorders Associated with the Sickle Cell Trait. S. Rahimtoola, C. J. Good, and P. D. B. Davies.
Plastic Bronchitis. R. Sleigh Johnson and E. G. Sita-Lumsden.
Mediastinal Teratomata. B. T. Le Roux.
Primary Intrathoracic Neural Tumours. B. T. Le Roux.
Collapse of the Lung Associated with Primary Tuberculosis: A Review of 51 Cases. A. Margaret C. Macpherson, P. A. Zorab, and Lynne Reid.
Index.

Volume 15, No. 4. (Quarterly; £4 annually.)

BRITISH JOURNAL OF OPHTHALMOLOGY

Pressure Changes in the Ophthalmic Artery after Carotid Occlusion. V. H. Smith.
Penicillin-Streptomycin-Gelatine Discs in the Treatment of Hypopyon Ulcers. A. D. Grover.
Experience with Twelve Cases of Intra-ocular Anterior Chamber Implants for Aphakia. J. Boberg-Ans.
Dark Adaptation Following Exposure to High-luminance Flashes. C. D. B. Bridges.
Two-stage Intracranial and Orbital Operation for Glioma of the Optic Nerve. N. S. Jain.
New Plastic Operation for Correcting the Refractive Error of Aphakic Eyes by Changing the Corneal Curvature. T. Krwawicz.
Juvenile Familial Mosaic Degeneration of the Cornea Associated with Megalocornea. B. Boles Carenini.
The Fight Against Trachoma in the Island of Malta. F. J. Damato.
Miniature Ophthalmic Diathermy Machine. P. A. Graham and A. Stanworth.
The Handle of the Cataract Knife. H. Lytton.
Reviews.

Volume 45, No. 1. (Monthly; £6 annually. With *Ophthalmic Literature* and Index, £9.)

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Application should be made first to the institution concerned.

Monday, January 16

CAMBRIDGE MEDICAL SOCIETY and BRITISH DENTAL ASSOCIATION (CAMBRIDGE SECTION).—At Farmers' Club, Owen Webb House, Gonville Place, Cambridge, 8.15 p.m., joint meeting. Dr. H. A. Fleming: The Cardiologists' Work in 1961. To be preceded by informal dinner at 7 p.m.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor Sheila Sherlock: Cirrhosis of Liver.

UNIVERSITY COLLEGE LONDON: DEPARTMENT OF PHARMACOLOGY.—At Physiology Theatre, Gower Street, W.C., 5.30 p.m., public lecture by Professor F. Bergel, F.R.S.: Biochemistry and Biology of Enzymes in Cancer.

Tuesday, January 17

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. R. G. Bannister: Anhidrosis and Heat Illness.

ILFORD MEDICAL SOCIETY.—At King George Hospital, Ilford, 8.45 p.m., Sir Daniel Davies: Perils of Mechanization in Medicine.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Goulstonian Lecture by Dr. D. A. Pond: Psychiatric Aspects of Epileptic Brain-damaged Children.

ROYAL COLLEGE OF SURGEONS OF ENGLAND.—5 p.m., Erasmus Wilson Demonstration by Dr. D. C. Caldwell: Radioactive Isotopes in a Chemical Laboratory.

ST. MARY'S HOSPITAL MEDICAL SCHOOL.—At Lecture Theatre, Wright-Fleming Institute, 5 p.m., Dr. H. Gardiner-Hill: Obesity in Women.

Wednesday, January 18

BONE AND TOOTH SOCIETY.—At 234 Great Portland Street, London W., 4.30 p.m., subject: Temporo-mandibular Joint.

HARVEIAN SOCIETY OF LONDON, 11 Chandos Street, W.—8.15 p.m., annual general meeting; 8.30 p.m., Presidential Address by Mr. T. E. Cawthorne: Medicine in Art.

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. O. Oliver: Modern Methods of Sterilization

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. N. Lloyd Rusby: Sarcoidosis.

INSTITUTE OF UROLOGY.—4.30 for 5 p.m., Mr. D. M. Wallace: Cancer of the Bladder.

LONDON ASSOCIATION OF THE MEDICAL WOMEN'S FEDERATION.—At Royal Free Hospital School of Medicine, 8 for 8.30 p.m., Miss I. H. Granger, M.A., will speak on the work of the Council.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. L. G. Lajtha: Culture of Bone Marrow.

ROYAL FREE HOSPITAL, Gray's Inn Road, London W.C.—5.15 p.m., Professor J. McMichael, F.R.S.: The Lungs in Heart Disease.

WILLESDEN GENERAL HOSPITAL MEDICAL SOCIETY.—At Department of Physical Medicine and Rheumatism, 8.30 p.m., Dr. T. C. Hunt: Atypical Peptic Ulcer.

Thursday, January 19

BELMONT HOSPITAL CLINICAL SOCIETY.—8 p.m., Dr. Robert Audrey: Role of the Father in the Family.

BRITISH INSTITUTE OF RADIOLOGY.—8 p.m., Treatment of the Reticuloses by Chemotherapy and Radiotherapy. Speakers, Dr. P. E. Thompson Hancock, Dr. J. D. N. Nabarro, and Dr. P. B. Kunkler.

BRITISH MEDICAL ASSOCIATION.—At B.M.A. House, Tavistock Square, London W.C., 5 for 5.30 p.m., lecture-discussion to be opened by Professor J. H. Kellgren: Diagnosis and Treatment of Osteoarthritis.

BRITISH POSTGRADUATE MEDICAL FEDERATION.—At London School of Hygiene and Tropical Medicine, 5.30 p.m., Dr. P. N. Magee: Biochemical and Pathological Mechanisms in Experimental Liver Cancer.

LIVERPOOL MEDICAL INSTITUTION.—Pathological Meeting. Dr. W. H. Taylor: Recent Developments in the Study of Gastric Function in Disease.

LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At Medical Society of London, 8.15 p.m., Professor Alexander Haddow: Present Situation in Cancer Research.

NUFFIELD ORTHOPAEDIC CENTRE.—At Wingfield-Morris Orthopaedic Hospital, Oxford, 8.30 p.m., Mr. W. J. W. Sharrard: Place of Orthopaedic Surgery in Cerebral Palsy.

ROYAL COLLEGE OF PHYSICIANS OF LONDON.—5 p.m., Goulstonian Lecture by Dr. D. A. Pond: Psychiatric Aspects of Epileptic Brain-damaged Children.

ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—At 26 Portland Place, London W., 7.30 p.m., Dr. T. Wilson: Filariasis in Malaya. A discussion will follow.

ST. ANDREWS UNIVERSITY.—At Physiology Department Lecture Theatre, 5 p.m., Professor G. A. Smart: Auto-immune Thyroiditis.

ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Sir Paul Mallinson: postgraduate demonstration in psychiatry.

Friday, January 20

BRITISH INSTITUTE OF RADIOLOGY.—At 32 Welbeck Street, London W., 2.30 p.m., Dr. M. Cohen, Ph.D., A.R.C.S.: Some Impressions of Radiation Physics and Radiotherapy in Scandinavia.

FACULTY OF RADIOLOGISTS.—At Royal College of Surgeons of England, 4.30 p.m., Radiotherapy Section Meeting. Professor D. W. Smithers, Dr. D. H. Nelson, Dr. Martin Bodian, and Dr. H. J. Whiteley: Spontaneous Regression of Tumours.

GALENICALS.—At Royal Fort, Bristol, 5.30 p.m., Dr. Macdonald Critchley: Medical Aspects of Oscar Wilde.

● INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. G. C. Wells: clinical demonstration.

INSTITUTE OF DISEASES OF THE CHEST.—5 p.m., Dr. K. Citron: clinical demonstration.

INSTITUTE OF LARYNGOLOGY AND OTOLOGY.—3.30 p.m., clinical discussion for general practitioners. Mr. Wallace Black: Vasomotor and Allergic Rhinitis.

LIVERPOOL SOCIETY OF ANAESTHETISTS.—At Liverpool Medical Institution, 8 p.m., Dr. A. H. Galley: Dental Anaesthesia, Past, Present, and Future.

PLYMOUTH MEDICAL SOCIETY.—At North Friary House, 8.30 p.m., Professor J. Chassar Moir: Some English Queens and their Confinements.

POSTGRADUATE MEDICAL SCHOOL OF LONDON.—(1) 10 a.m., Mr. Wylie McKissock: Some Aspects of the Surgery of Intracranial Haemorrhage. (2) 4 p.m., Dr. M. D. Milne: Renal Tubular Transport Defects.

Saturday, January 21

ANGLO-AMERICAN MEDICAL SOCIETY.—At U.S.A.F. Base, Alconbury, near Huntingdon, 2 p.m., conducted tour of Base; cocktails and buffet; Dr. Julian Ward (Medical Adviser, U.S. Pioneer Space Project): Medical Aspects of Space Travel.

SOUTH-EAST METROPOLITAN REGIONAL TUBERCULOSIS SOCIETY.—At Evelina Children's Hospital, Southwark Bridge Road, 10.30 for 11 a.m., joint meeting with South-east Metropolitan Regional Paediatric Society. Discussion to be opened by Dr. Owen Clarke, Dr. P. Swift, and Dr. M Nagley: The Chesty Child.

Sunday, January 22

COLLEGE OF GENERAL PRACTITIONERS: YORKSHIRE FACULTY.—At Littlewood Hall, General Infirmary at Leeds, 11 a.m., Pfizer Lecture by Dr. W. Whitaker: Selection of Cardiological Patients for Surgical Treatment.

APPOINTMENTS

BEARE, R. L. B., F.R.C.S., Consultant Plastic Surgeon at St. Mary's Hospital, London W., and at the Plastic Surgery and Jaw Injury Centre, Queen Victoria Hospital, East Grinstead, Sussex.

DAVIDSON, W. G., M.D., D.P.H., D.T.M.&H., Medical Officer to Usutu Pulp Co., Mhlambanyati, Swaziland.

HOSPITAL FOR SICK CHILDREN, Great Ormond Street, London, W.C.—J. S. Gupta, M.B., B.S., F.R.C.S., D.O.M.S., Part-time Medical Officer to Ophthalmic Department; F. P. A. Capps, M.B., B.S., D.Obst.R.C.O.G., and G. S. Gilchrist, M.B., B.Ch., House-physicians.

MANCHESTER REGIONAL HOSPITAL BOARD.—J. B. Macmillan, M.B., Ch.B., F.R.F.P.S., Consultant Dermatologist (eight half-days), Blackpool and Fylde, Preston and Chorley, Blackburn and District, and Burnley and District Groups of Hospitals; J. R. Theobalds, M.R.C.S., L.R.C.P., D.P.M., Whole-time Assistant Psychiatrist, Lancaster Moor Hospital; M. H. Hall, M.R.C.S., L.R.C.P., Whole-time Senior Accident Officer, Preston Royal Infirmary.

NORTH-WEST METROPOLITAN REGIONAL HOSPITAL BOARD.—V. L. Steinberg, M.B., B.S., M.R.C.P.Ed., D.Phys.Med., Consultant Physician in Physical Medicine, Central Middlesex Hospital; E. V. Slaughter, F.F.A. R.C.S., M.R.C.S., L.R.C.P., Consultant Anaesthetist, Acton and Neasden Hospitals; T. M. Ness, M.B., Ch.B., F.F.A. R.C.S., Consultant Anaesthetist, Archway Group; J. I. Pugh, M.D., Consultant Pathologist (Morbid Anatomy), Mid-Herts Group of Hospitals; Beryl G. Anscombe, M.B., Ch.B., D.P.M., D.Obst.R.C.O.G., Assistant Psychiatrist (S.H.M.O.), Napsbury Hospital; A. Benjamin, M.B., B.S., F.R.C.S., Consultant Traumatic and Orthopaedic Surgeon, Watford Peace Memorial and West Herts Hospitals; A. K. Graf, M.D., D.P.M., Consultant Psychiatrist, Willesden and Hornsey Child Guidance Centres.

SPENCER (formerly BACON), Pamela M., M.B., B.S., F.R.C.S., M.R.C.O.G., Second Honorary Gynaecologist, Italian Hospital, Queen Square, London, W.C.

WOLF, LEONARD M., M.B., B.Ch., M.R.C.O.G., Assistant Gynaecological Surgeon, Beekman-Downtown Hospital, New York; Assistant Obstetrician and Gynaecologist, French Hospital, New York; Clinical Assistant in Obstetrics and Gynaecology, Mount Sinai Hospital, New York.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Bolton.—On December 31, 1960, at Oxford, to Joyce, wife of Dr. F. G Bolton, a son.

DEATHS

Burn.—On December 18, 1960, Alfred Burn, M.D., of Lothian, Baldwin Avenue, Eastbourne, Sussex, formerly of Crawley, Sussex.

Carr.—On December 2, 1960, Arthur Carr, M.R.C.S., L.R.C.P., of 88 Brick Lane, London E., aged 55.

Farnfield.—On December 5, 1960, at Royal East Sussex Hospital, Hastings, Sussex, John Stewart Farnfield, M.R.C.S. L.R.C.P., of 183 Ashburnham Road, Hastings, aged 83.

Harrison-Cripps.—On December 13, 1960, at his home, Meath Green House, Horley, Surrey, William Lawrence Harrison-Cripps, M.B., F.R.C.S., aged 82.

Herbert.—On December 5, 1960, at his home, Noel Morley Herbert, L.R.C.P.&S.I. and L.M.

Hoskyn.—On December 17, 1960, at St. Bartholomew's Hospital, London E.C., Charles Henry Hoskyn, O.B.E., M.D., D.P.H., D.I.H., of 51 Hampstead Way, London N.W., aged 48

Kirby.—On December 18, 1960, at his home, 295 Dyke Road, Hove, Sussex, Paul Rustat Ellis Kirby, M.R.C.S., L.R.C.P.

Lacks.—On December 19, 1960, Frederick Siegfried Lacks, L.R.C.P.&S.Ed., L.R.F.P.S., of 335 Wilbraham Road, Manchester.

Leahy.—On December 10, 1960, at his home, Sunninghill, Berks, James Daly Leahy, *M.C.*, M.B., B.Ch., Air Commodore, R.A.F., retired.

Mackenzie.—On December 17, 1960, Derek St. Clair Mackenzie, M.B., B.Ch., of Fulwood, Sandycombe Road, Kew, Surrey, aged 58.

Moore.—On November 25, 1960, William A. Moore, M.B., B.Ch., of Freshford, Co. Kilkenny.

Nichol.—On December 8, 1960, at 87 Woodstock Road, Oxford, Frances Louisa Nichol, M.B., B.S.

Shelton.—On December 9, 1960, in hospital, Charles Frank Shelton, M.D., M.R.C.P., D.T.M.&H., late of East Africa.

Smith.—On December 6, 1960, Montague Smith, M.R.C.S., L.R.C.P., of 18 Queen Elizabeth Drive, Southgate, London N., late of Kenninghall Road, Clapton, London E., aged 87.

Smyth.—On December 17, 1960, Frederick Gerald Smyth, M.B., B.Ch., of 2A Royal Road, St. Albans, Herts.

Sykes.—On December 17, 1960, at his home, Ashhurst, Formby, Lancs, Arthur Barry Sykes, M.R.C.S., L.R.C.P., aged 84.

Whitby.—On December 13, 1960, Joseph Whitby, M.D., M.R.C.P., D.P.H., D.P.M.

Wood.—On December 17, 1960, at Stratford Tony House, Salisbury, Wilts, Robert Lucius Wood, M.D., formerly of Knowsley, Lancs, aged 90.

Young.—On December 1, 1960, at Newbury, Berks, Graham Pallister Young, M.B., B.S.

Any Questions ?

We publish below a selection of those questions and answers which seem of general interest. It is regretted that it is not possible to supply answers to all questions submitted.

Relative Lymphocytosis

Q.—*What is the significance of relative lymphocytosis in apparently otherwise normal people? Do children with this condition revert to a normal blood count? Have people with a relative lymphocytosis a reduced resistance to disease? What is the white cell response to infection?*

A.—A relative lymphocytosis implies an increase in the percentage but not the absolute number of lymphocytes in a differential white cell count, and therefore is found in conditions producing a polymorphonuclear leucopenia. In an apparently otherwise normal person this may signify a wide range of pathological states, including active or convalescent viral, bacterial, protozoal, and fungal diseases, collagen disorders, depression of the granulocytes and precursors in the bone marrow in the blood disorders, and the so-called hypersplenism.

Children normally have a greater number of lymphocytes than granulocytes in their peripheral blood, lymphocytosis being normal in the first five years. By the age of 5 years the numbers of lymphocytes and polymorphs are approximately equal and reach adult proportions by ten years.

The patient's resistance to disease will depend on the nature and cause of the relative lymphocytosis—conditions producing severe polymorphonuclear leucopenia will predispose to a lesser degree of resistance to infections. In general, leucocytes respond to bacterial infections by polymorphonuclear leucocytosis, to viral infections by lymphocytosis, and to protozoal attack by monocytosis. However, these broad generalizations may not hold in any particular case. The factors modifying the response include genus of organism involved, its virulence, size of infecting dose, and host resistance. Children commonly respond to infection with a lymphocytosis.

Treatment of Angioneurotic Oedema

Q.—*What is the present-day treatment of angioneurotic oedema?*

A.—The treatment of angioneurotic oedema is as for urticaria. The cause may be discovered by a careful history, by keeping a diary of events, or by intradermal skin tests. The cause is sometimes emotional or dependent upon physical factors. In a proportion of patients no cause is found. Sometimes the affection is familial and hereditary, and here there is a more serious risk of oedema of the larynx, which may prove fatal. Immediate treatment is by injection of adrenaline or pituitrin or by sucking isoprenaline tablets.

Quinine in Malignant Tertian Malaria

Q.—*What, if any, is the place of quinine in the treatment of malignant tertian malaria?*

A.—The main disadvantages of quinine leading to its replacement by other antimalarials are: (1) that it is slower in action against schizonts than is chloroquine, amodiaquine, or mepacrine; (2) that, particularly in the case of chronic *Plasmodium falciparum* infections, its use may precipitate blackwater fever; (3) that, even in maximally tolerated doses, its suppressive action is unreliable; and (4) its cost per treatment is slightly greater than that of chloroquine.

In treating acutely ill patients, the increased speed of action of chloroquine may be life-saving, and many thousands of lives have also been saved by obviating blackwater fever, which was a not uncommon complication of attempted quinine suppression or treatment of *P. falciparum* infections. It is possible that intravenous injections of chloroquine give rise to a slightly greater lowering of the blood-pressure than do similar injections of quinine, but this untoward effect can be obviated by giving injections slowly or by administering the therapeutic dose in 1 pint (0.6 litre) of normal saline solution introduced intravenously by a drip infusion. In this connexion, patients requiring intravenous antimalarial therapy almost invariably also require intravenous fluids.

In the light of these considerations, quinine is now generally recommended in *P. falciparum* infections only for intravenous injections to those who are severely ill and for whom chloroquine cannot be obtained.

Reserpine and Lactation

Q.—*An 18-year-old girl, suffering from primary dysmenorrhoea, was given reserpine 0.25 mg. three times a day, starting in mid-cycle and terminating at onset of menstruation. It produced the rather disturbing side-effect of lactation. What is the mechanism of this?*

A.—Swelling of the breasts and lactation are recognized[1,2] but rather infrequent side-effects of treatment with reserpine. Experimental work in animals[3–6] suggests that these effects are the result of an increased secretion of the hormone prolactin from the pituitary gland. The administration of reserpine alone does not cause mammary growth or lactation but does increase the prolactin content of the pituitary gland. If the animals are primed by giving them oestrogens for several days before the administration of reserpine, then mammary growth, with development of the ducts and the alveoli, is observed and lactation may occur. It would thus appear that the mechanism of this side-effect in man is probably the presence of a sufficient concentration of reserpine at a critical stage in the menstrual cycle. It is worth noting that the opposite effect—namely, suppression of lactation—in a woman in the puerperium who was receiving reserpine for hypertension, has also been recorded.[7] In this case the mechanism was probably fluid retention in the tissues with consequent drying up of the milk supply.

REFERENCES

1 Platt, R., and Sears, H. T. N., *Lancet*, 1956, **1**, 401.
2 Robinson, B., *Med. J. Aust.*, 1957, **2**, 239.
3 Meites, J., *Proc. Soc. exp. Biol.*, 1957, **96**, 728.
4 —— ibid., 1958, **97**, 742.
5 —— Nicoll, C. S., and Talwalker, P. K., ibid., 1959, **101**, 563.
6 Grönroos, M., Kalliomäki, J. L., Keyriläinen, T. O., and Marjanen, P., *Acta endocrinol.*, 1959, **31**, 154.
7 Woolman, A. M., *Lancet*, 1956, **1**, 690.

Eliminating House-dust

Q.—*A patient suffering from asthma has a marked skin sensitivity to house-dust. What practical measures can be adopted to eliminate dust from the bedroom? Is there any method of treating blankets and carpets to prevent them storing dust?*

A.—Measures to eliminate dust from a bedroom are as follows. The mattress should be of rubber and the pillows should also be of rubber or "terylene." Sheets should be of cotton or nylon. Blankets and quilts should be of terylene or other synthetic material, although flannelette or woollen blankets are usually allowed, with the advice that they should be laundered or dry-cleaned every two or so weeks.

The bedroom floor should be bare or covered with linoleum and polished daily, or oiled to give it a slightly sticky surface. Nylon rugs can be used, although small washable ordinary rugs are usually permitted. Furniture (including ornaments, pictures, and toys) should be reduced to a minimum. A special dusting of the bedroom should be carried out with a damp cloth every other day, especially over the top of high furniture, picture rails, etc., where dust tends to accumulate. Oiling of woollen blankets and carpets, if used, will reduce dust, but whether the cost and inconvenience make it a worth-while procedure is doubtful.[1]

REFERENCE

1 *Brit. med. J.*, 1949, **2**, 1539.

Collecting Vaginal Pathogens

Q.—*Is there any technique whereby all vaginal pathogens, including trichomonas vaginalis, can be detected by taking a vaginal swab, and not a pipette specimen, to the pathological laboratory?*

A.—When the discharge is sufficiently copious, it is best to collect it direct into a sterile container. For general purposes, however, it suffices to take an ordinary swab in a test-tube containing an amount of sterile saline just sufficient for the tip of the swab to remain moistened. In all cases the sooner the specimen is available to the pathologist the better. If, however, a gonococcal infection is to be excluded, for instance, in vulvovaginitis in infants, inoculation of a Stuart's transport medium[1] with a charcoal swab of the discharge allows identification of the gonococci even if there is some delay—e.g., transmission by post—in the specimen reaching the laboratory. The questioner might do best to seek advice on these or other swabs and materials from the pathologist to whom he is going to submit the specimens.

REFERENCE

1 Stuart, R. D., Toshach, S. R., and Patsula, T. M., *Canad. J. publ. Hlth*, 1954, **45**, 73.

Peyronie's Disease

Q.—*A man aged 53 states that his glans penis tilts strongly to the left when erected. This has happened for only one month, and he states that the glans is definitely erectile, as is the corpus of the penis. There appears to be no abnormality on examination in the normal state. What is the cause of this?*

A.—The onset of a chordee in a man of this age without any relevant history of injury or inflammation is nearly always due to a plaque of Peyronie's disease. In the early stages the nodules may be extremely small and difficult to locate in the corpora, but they are generally easily palpable once their presence is suspected or the site of angulation can be accurately localized by the patient.

Peyronie's disease, or plastic induration of the penis, is much more common than is generally realized. The lesion consists in a condensation of fibrous tissue within the tunica albuginea of the corpora cavernosa. The nodules may be single or multiple, and they vary in size from a match-head or less up to two or three inches (5–7.5 cm.) in length. Apart from the chordee, erection may be painful, but there is no interference with the urinary flow, and the patient can be reassured that this is a non-malignant condition.

In spite of the many theories put forward to explain the aetiology, it would be safer to admit that we do not yet know the cause of this lesion. Treatment may be equally unsatisfactory, but the administration of cortisone has produced good results in some cases.[1] An excellent review of the pathology of these fibrotic lesions has recently been given by Pugh.[2]

REFERENCES

1 Chesney, J., 1960, pending publication.
2 Pugh, R. C. B., *Proc. roy. Soc. Med.*, 1960, **53**, 685.

Douching for Infertility

Q.—*It is said that douching with Ringer–Locke's solution, to which a little dextrose is added, is of use in the treatment of infertility. Is this method still in favour?*

A.—This form of treatment stems from an article by J. MacLeod and R. S. Hotchkiss.[1] It is based on the fact that, according to *in vitro* studies, spermatozoa require not less than 20 mg. % glucose in their environment in order to retain their motility. The nutritive carbohydrate normally present in seminal fluid is fructose. So, with the object of prolonging life and activity of spermatozoa in the female genital tract, either glucose or fructose can be placed in the vagina before coitus. This is done by douching with either Ringer or Ringer–Locke's solution to which is added one or other of these carbohydrates in a strength of 20 g. per litre. It is also argued that such a solution may make the cervical plug of mucus more penetrable. How much carbohydrate is deposited by this technique is obviously questionable; moreover, if much douche fluid is retained in the vagina it might adversely dilute the seminal pool.

The treatment is empirical and of doubtful value, so it is not very popular. There is, however, no harm in trying it when all else fails. On theoretical grounds it might be indicated in those cases where semen analysis shows oligospermia and spermatozoa of poor motility, especially if the fructose content of the seminal fluid is less than normal. The normal value is of the order of 300 mg./100 ml. at the time of ejaculation, falling rapidly during the ensuing hours as it is utilized by the spermatozoa.

REFERENCE

1 MacLeod, J., and Hotchkiss, R. S., *Amer. J. Obstet. Gynec.*, 1943, **46**, 424.

Inheritance of Haemophilia

Q.—*A patient who is pregnant has two aunts on her mother's side who have each given birth to a male child suffering from haemophilia. There is no bleeding tendency in the husband's family and I cannot obtain any evidence of blood disease in any other member of her mother's family. What are the chances of this baby being affected?*

A.—On the information given, the probability that the patient's mother is a carrier of haemophilia is 1 in 2, and that the patient herself is a carrier is 1 in 4. The risk that a male child of the patient's will have haemophilia, or that a female child will be a carrier, is 1 in 8. If the patient has unaffected brothers, or sisters with unaffected sons, this would reduce the probability that the patient's mother is a carrier, and the risks for the patient's sons.

Antibodies in Second Pregnancy

Q.—*If tests at 34 weeks and at delivery show no antibodies in an Rh-negative patient, when should tests be repeated during the next pregnancy?*

A.—Rh-antibodies should be tested for when the patient is first seen in her next pregnancy, for if they are then present she should be booked for confinement in hospital. In addition, the titre of antibody then present can be used as a baseline against which to compare test results at the 34th week and later, if such quantitative estimations are made in the area in which the inquirer practises. If there are no antibodies present at the time of the first test, a further blood test should be carried out at the 32nd to 34th week.

NOTES AND COMMENTS

Napkin-rash.—Dr. I. PATRICIA BROWN (Newcastle upon Tyne 6) writes: As a mother of four children I must comment on Dr. Mary N. M. Paulin's advice (December 31, p. 1970) to destroy bacteria in napkins by overnight soaking in ordinary domestic bleaching agents. I am afraid she would find little left of her napkins in the morning. Two solutions to the problem I have found: disposable napkins, if the patient can afford them, or steeping the napkins in benzalkonium chloride.

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